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Health and Environmental Effects Profile for Hexachlorophene

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16. ABSTRACT

The Health and Environmental Effects Profile for Hexachlorophene was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Hexachlorophene has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for hexachlorophene is 0.001 mg/kg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for hexachlorophene is 100.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR HEXACHLOROPHENE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3112. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

EXECUTIVE SUMMARY

Hexachlorophene is an odorless, white, powdery solid that is practically insoluble in water, but soluble in most organic solvents (Sax, 1984). Being a weak acid, it forms salts with alkalies and ionizes at high pH. When heated to decomposition, hexachlorophene emits highly toxic fumes. As of January 1984, Givaudan Corp. was the only manufacturer of hexachlorophene in the United States (USITC, 1984), although production may have ceased in 1985 (SRI, 1985). Hexachlorophene may contain $\leq$0.03 µg/g of the highly toxic chemical, 2,3,7,8-TCDD (Rappe et al., 1979). The waste materials generated in still bottoms and in filter cakes during the manufacture of hexachlorophene may contain higher levels of 2,3,7,8-TCDD. The disposal of these waste materials should be carefully controlled.

Relatively high concentrations of hexachlorophene (~3%) were used in the past in cosmetic and toiletry preparations as an antimicrobial agent. Present use in drug and cosmetic products is restricted to $\leq$0.1%. In certain cases, use of hexachlorophene is approved for surgical scrubbing and handwashing in hospitals. The monosodium salt of hexachlorophene is used in fungicide preparations for limited crops.

Pertinent data regarding the fate of hexachlorophene in the atmosphere were not located in the available literature. Based on its physico-chemical properties, hexachlorophene may be present in the atmosphere in the particulate-sorbed state. Dry deposition may be an important physical mechanism for removal from the atmosphere; however, this chemical is likely to persist in the atmosphere. In the aquatic environment, degradation of hexachlorophene by hydrolysis, photolysis or biodegradation is likely to be insignificant (Moore and Tamat, 1980; Shaffer et al., 1971; Van Auken and Hulse,

1978a, 1979; Silberman, 1975; Lee and Ryan, 1978). The BCF of hexachlorophene in mosquito fish, Gambusia affinis, was 278 (Sanborn, 1974); therefore, significant bioconcentration of hexachlorophene in edible aquatic organisms is unlikely. The compound may not volatilize significantly from water, but will be associated with the suspended particulates and sediments in aquatic environments (Buhler et al., 1973; Sims and Pfaender, 1975). Thus, hexachlorophene probably persists in the aquatic environment. Hexachlorophene was immobile ir most soils tested (Helling et al., 1974). Based on its fate in water, photolysis, hydrolysis or evaporation or hexachlorophene in soil is probably insignificant. Whether biodegradation of hexachlorophene in soil is fast enough to prevent it from leaching into groundwater is not known. Hexachlorophene is likely to persist in soil.

Pertinent data regarding the atmospheric level of hexachlorophene were not located in the available literature. Hexachlorophene has been detected in urban surface water and in surface water downstream from sewage treatment plants at concentrations $\leq$44.3 ppb (Sims and Pfaender, 1975). In a study of the drinking water in Corvallis, OR, the level of hexachlorophene was 0.01 ppb (Buhler et al., 1973). Hexachlorophene at concentrations <2-9.5 ppb has been detected in the milk of nursing women. No hexachlorophene was found in commercial cow's milk (West et al., 1975). Hexachlorophene has been detected in the tissues of hospital patients and physicians who use products containing hexachlorophene. The levels in the blood of hospital surgical personnel was 0.07-0.22 µg/g, compared with a level of 0.03 µg/g in a control group (Butcher et al., 1973). Human adipose tissue from the neck and abdomen of random individuals showed mean hexachlorophene levels of 0.01 and 0.04 µg/g of tissue, respectively (Ulsamer et al., 1973).

Hexachlorophene appears to be rapidly and nearly completely absorbed from the gastrointestinal tract (Kennedy et al., 1977; Bjondahl and Isomaa, 1976; Gandolfi and Buhler, 1974, 1977) and through the vaginal mucosa (Chow et al., 1978b; Kimmel et al., 1974). Dermal absorption in experimental animals appears to be extensive, but somewhat slower than absorption following oral administration (Kennedy et al., 1977; Nakaue and Buhler, 1976; Chow et al., 1978a). In humans, particularly in infants, dermal exposure has lead to severe intoxication and fatalities (Chilcote et al., 1972, 1977; Anderson et al., 1975; Goutieres and Aicardi, 1977; Tyrala et al., 1977; Gillespie et al., 1974; Kopelman, 1973; Cunningham and Tsoulos, 1972).

Distribution of hexachlorophene is primarily to the blood, where the majority of the dose is bound to plasma protein, and to highly vascular organs such as the liver, kidney and placenta (Chow et al., 1978a; Brandt et al., 1979, 1983; Nakaue and Buhler, 1976). Relatively low levels are found in the brain. Distribution also occurs to the fetus, generally at levels lower than those observed in maternal blood and tissues (Brandt et al., 1979, 1983; Kimmel et al., 1974; Kennedy et al., 1977). Distribution to neonates also occurs through the mother's milk (Kennedy et al., 1977; Gaines et al., 1973).

The major metabolite of hexachlorophene is hexachlorophene monoglucuronide, which occurs as $\geq$90% of the radioactivity in bile and urine of ^{14}C-hexachlorophene treated rats and rabbits (Gandolfi and Buhler, 1974, 1977). The liver is very important in the metabolism and excretion of hexachlorophene.

Excretion is primarily by the biliary route, and considerable enterohepatic recirculation occurs (Gandolfi and Buhler, 1974; Edelson and McMuller, 1976). Urinary excretion is a minor pathway of elimination

(Gandolfi and Buhler, 1974, 1977; Chow et al., 1978a); hexachlorophene and its metabolites are excreted in the gastrointestinal tract (Gandolfi and Buhler, 1974).

Hexachlorophene was negative for carcinogenicity in at least two strains of rats (NCI, 1978; Rudali and Assa, 1978; IRDC, 1980a) and at least two strains of mice (Rudali and Assa, 1978; IRDC, 1980b) in lifetime feeding experiments. In addition, negative results were obtained in mice exposed during gestation or in the neonatal period. Lifetime skin painting tests were negative in mice and rabbits (Stenback, 1975, 1977).

Hexachlorophene was consistently negative for mutagenicity when tested in the S. typhimurium assay (Haworth et al., 1983; Arnold et al., 1975; Gocke et al., 1981), chromosomal aberration tests (Dymin et al., 1984; Gocke et al., 1981; Sobti et al., 1983), the dominant lethal test in male mice (Kennedy et al., 1975a; Arnold et al., 1975) and the sex-linked recessive test in D. melanogaster (Gocke et al., 1981). Positive results were noted only in experiments in two Eastern bloc countries: a test in S. typhimurium (Dymin et al., 1984) and a micronucleus test in mouse bone marrow cells (Syllanco, 1978); the data were not presented in either of these two reports.

Hexachlorophene was discovered to be fetotoxic and teratogenic to rats treated orally (Oakley and Shepard, 1972; Kennedy et al., 1975b) or vaginally (Kimmel et al., 1972, 1973, 1974), in rabbits treated orally (Kennedy et al., 1975b) and in hamsters treated subcutaneously (Geber, 1977). Mice treated dermally exhibited fetotoxicity but not teratogenicity. The threshold for teratogenicity by the oral route appears to be ~25 mg/kg/day in rats (Oakley and Shepard, 1972) and ~6 mg/kg/day in rabbits (Kennedy et al., 1975b). In rats, a dose of 15 mg/kg/day is associated with fetotoxicity (Kennedy et al., 1976b; Haley et al., 1973). Maternal toxicity is also associated with the same dose levels that cause teratogenicity.

Hexachlorophene has been implicated as a human teratogen, primarily because of retrospective studies of malformed infants born to Swedish hospital workers exposed to the chemical (Halling, 1977, 1979). A subsequent and longer epidemiological study, however, failed to find an increased incidence of malformed infants born to hexachlorophene-exposed hospital workers (Baltzar et al., 1979a).

In a reproduction study, hexachlorophene at 10 mg/kg/day by gavage (Kennedy et al., 1976b) reduced the survival of 12- and 21-day-old offspring in rats. In a 3-generation feeding study in rats, decreased numbers of corpora lutea and implantations, decreased numbers of F_{1a} pups surviving until lactation day 4 and decreased body weight of pups were observed at 60 ppm (IRDC, 1979). Hexachlorophene administered to mature male dogs and rats at $\geq$3 mg/kg/day for 9 weeks or to rats at single doses $\geq$75 mg/kg brought about a rapid but transitory reduction in spermatogenesis and degeneration of the germinal epithelium of the testes (Thorpe, 1967; James et al., 1980). Hexachlorophene administered subcutaneously to neonatal hamsters (Alleva, 1973) or dermally to rats (Gellert et al., 1978) had no effect on the subsequent sexual maturation or fertility of the hamsters or female rats. Male rats, however, had severely depressed fertility, resulting primarily from an inability to ejaculate; spermatogenesis appeared to be normal.

Chronic toxicity tests with hexachlorophene include the NCI (1978) bioassay in rats, the Rudali and Assa (1978) assays in rats and mice and the IRDC (1980a,b) studies in rats and mice. No adverse effects were noted at dietary levels $\leq$150 ppm in rats or mice in the NCI (1978) and Rudali and Assa (1978) studies. The only effect observed in the IRDC (1980a,b) studies was reduced body weight gain in rats fed 100 ppm; food consumption data were not reported. Adverse effects were observed at lower doses in subchronic studies.

The central and peripheral nervous system and the retina appear to be the target tissues for the toxicity of hexachlorophene, as shown by several short-term studies performed at high doses. Subchronic oral studies in rats appear to define the following thresholds: death at 28.9 mg/kg/day, slowly reversible neurological dysfunction at 14.9 mg/kg/day, reduced rate of body weight gain at 7.7 mg/kg/day (Nakaue et al., 1973) and histopathological lesions in the nervous system at 5 mg/kg/day (Jones et al., 1974). These data suggest a relatively steep dose response curve for hexachlorophene. Neonates tend to be more sensitive than older nursing or adult rats (Ulsamer et al., 1975). Beagle dogs appear to be more sensitive than rats; at 30 ppm (0.75 mg/kg/day) in the diet for 13 weeks, dogs had "status spongiosis" of the brain and optic nerve (IRDC, 1974).

Newborn pigs appear to be the most sensitive animal model tested, as the threshold for death and histopathological lesions of the brain appears to be 1-2 mg/kg/day and the threshold for mild neurological signs appears to be 0.5 mg/kg/day (Robinson et al., 1975). No effects were observed at 0.1 mg/kg/day.

Oral LD_{50} values in rats range from 9-200 mg/kg/day with adults being more resistant than neonates (Nieminen et al., 1973; Dymin et al., 1984). Pigs appear to be the most susceptible species tested, as the oral LD_{50} is 4 mg/kg for newborn pigs (O'Donoghue, 1985).

The neurological signs and histopathological lesions produced in humans by accidental oral or dermal intoxication closely resemble those observed in experimentally poisoned animals. In cases of oral poisoning, severe gastrointestinal signs also occur (Powell and Lampert, 1979; Kimbrough, 1976).

The majority of human toxicity cases involve dermal exposure. Neonatal infants appear to be the subpopulation at greatest risk, and their susceptibility is increased by reduced birthweight, premature delivery or impaired liver function (Shuman et al., 1974b, 1975; Anderson et al., 1975, 1981; Plueckhahn and Collins, 1976). Burn victims are also at high risk to the dermal application of hexachlorophene (Chilcote et al., 1972, 1977).

Hexachlorophene was toxic to Daphnia magna, inhibiting reproduction at 0.008 mg/ℓ (Hattori et al., 1984).

An ADI of 0.001 mg/kg/day (0.07 mg/day for a 70 kg man) was derived from a NOEL of 0.1 mg/kg/day in newborn pigs (Robinson et al., 1975). An uncertainty factor of 100 was applied to extrapolate from animal to human data and to account for sensitive subgroups. An uncertainty factor was not applied to extrapolate from subchronic to chronic exposure because the evidence suggests that animals may develop tolerance with continued exposure that effects are reversible and do not progress with continued exposure.

A CS of 30.6, corresponding to an RQ of 100 associated with neurological dysfunction and CNS lesions in swine, was chosen to represent the chronic toxicity of hexachlorophene. Because of the lack of positive evidence for carcinogenicity, no potency factor was calculated. IARC (1979) declined to classify hexachlorophene as a potential carcinogen for humans because of the lack of data. An IARC ranking of Group 3, not classified, appears most appropriate. Based on U.S. EPA (1984) guidelines for carcinogen risk assessment, inadequate animal evidence and no human evidence is available for hexachlorophene. The overall weight of evidence classification of Group D, not classifiable as to human carcinogenicity, is suggested for hexachlorophene. It should be pointed out that hexachlorophene may be contaminated with the highly toxic chemical 2,3,7,8-TCDD (dioxin), considered by U.S. EPA to be a probable human carcinogen.

TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1
1.1.	STRUCTURE AND CAS NUMBER	1
1.2.	PHYSICAL AND CHEMICAL PROPERTIES	1
1.3.	PRODUCTION DATA	2
1.4.	USE DATA	3
1.5.	SUMMARY	3
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES	5
2.1.	AIR	5
2.2.	WATER	5
2.3.	SOIL	9
2.4.	SUMMARY	9
3.	EXPOSURE	11
3.1.	AIR	11
3.2.	WATER	11
3.3.	FOOD AND OTHER MEDIA	12
3.4.	OCCUPATIONAL LEVEL	13
3.5.	SUMMARY	13
4.	PHARMACOKINETCS	15
4.1.	ABSORPTION	15
4.2.	DISTRIBUTION AND RETENTION	20
4.3.	METABOLISM	23
4.4.	EXCRETION	26
4.5.	SUMMARY	28
5.	EFFECTS	31
5.1.	CARCINOGENICITY	31
5.2.	MUTAGENICITY	33
5.3.	TERATOGENICITY	34
5.4.	OTHER REPRODUCTIVE EFFECTS	40
5.5.	CHRONIC AND SUBCHRONIC TOXICITY	44
5.5.1.	Chronic Studies	44
5.5.2.	Subchronic Studies	46
5.6.	OTHER RELEVANT INFORMATION	51
5.7.	SUMMARY	55

TABLE OF CONTENTS (cont.)

	Page
6. AQUATIC TOXICITY	59
6.1. ACUTE	59
6.2. CHRONIC	59
6.3. PLANTS	59
6.4. RESIDUES	59
6.5. SUMMARY	60
7. EXISTING GUIDELINES AND STANDARDS	62
7.1. HUMAN	62
7.2. AQUATIC	62
8. RISK ASSESSMENT	63
9. REPORTABLE QUANTITIES	68
9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY	68
9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY	73
10. REFERENCES	74
APPENDIX: LITERATURE SEARCHED	97

LIST OF TABLES

No.	Title	Page
4-1	Uptake and Distribution of ^{14}C-Hexachlorophene in Rats 24 Hours After Treatment with 150 mg/kg	19
4-2	Tissue Residues of Radioactivity, Expressed as Hexachlorophene Equivalent, in Rats Treated Dermally with [^{14}C-Methylene]hexachlorophene.	22
4-3	Levels of Radioactivity, Expressed as Hexachlorophene Equivalent in Selected Compartments of Pregnant Rats Following Oral or Dermal Treatment with ^{14}C-Hexachlorophene	24
5-1	Mutagenicity and Genotoxicity of Hexachlorophene.	35
5-2	Teratogenicity and Fetotoxicity of Orally Administered Hexachlorophene	36
5-3	Multigeneration Reproduction Studies in Rats Fed Dietary Hexachlorophene	41
5-4	Subchronic Oral Toxicity Studies with Hexachlorophene	48
5-5	LD_{50} Values for Hexachlorophene	52
6-1	Hexachlorophene Concentrations in Water, Sediments and Aquatic Invertebrates in Upper Haw River Basin, NC.	61
9-1	Summary of Oral Teratogenicity and Reproductive Studies of Hexachlorophene in Laboratory Animals	69
9-2	Composite Scores for the Toxicity of Orally Administered Hexachlorophene	70
9-3	Hexachlorophene: Minimum Effective Dose (MED) and Reportable Quantity (RQ).	72

LIST OF ABBREVIATIONS

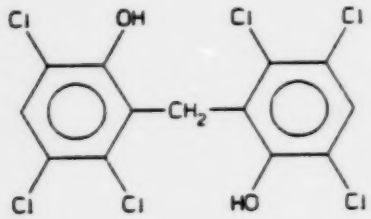
ADI	Acceptable daily intake
BCF	Bioconcentration factor
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
DMSO	Dimethyl sulfoxide
EC_{50}	Median effective concentration
EEG	Electroencephalogram
EPN	O-ethyl O-para-nitrophenyl phenylphosphonothioate $[C_6H_5P(C_2H_5O)(S)OC_6H_4NO_2]$
i.m.	Intramuscular
i.p.	Intraperitoneal
i.v.	Intravenous
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Median lethal concentration
LD_{50}	Median lethal dose
LH	Luteinizing hormone
MAD	Minimum active dose
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
ppb	Parts per billion
ppm	Parts per million
R_f	Ratio of solvent found to compound
RQ	Reportable quantity

RV_d	Dose-rating value
RV_e	Effect-rating value
s.c.	Subcutaneous
2,3,7,8-TCDD	2,3,7,8-Tetrachlorodibenzo-p-dioxin
TLC	Thin-layer chromatography
TWA	Time-weighted average

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The chemical commonly called hexachlorophene is also known as 2,2'-methylenebis(3,4,6-trichlorophenol); bis(2-hydroxy-3,5,6-trichlorophenyl)-methane; 2,2'-dihydroxy-3,3',5,5',6,6'-hexachlorodiphenylmethane; hexachlorofen; and trichlorophene. Some of the commonly used trade names for this compound are Acigena, Bilovon, Dermadex, Exofene, G-11, Gamophen, Hexafen, Nabac, Phisodan, HisoHex, Surofenen and Turgex (IARC, 1979). The structure, molecular weight, and empirical formula for hexachlorophene are as follows:



Molecular weight: 406.9

Molecular formula: $C_{13}H_6O_2Cl_6$

The CAS Registry number for this compound is 70-30-4.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Hexachlorophene is an odorless, white powdery solid. It is soluble in acetone, alcohol, ether, chloroform and dilute solutions of alkalies (Sax, 1984). The physical properties of hexachlorophene are listed below:

Melting point:	166-167°C	IARC, 1979
pKa at 25°C:	4.95	Hansch and Leo, 1985
Water solubility at 25°C:	1.7×10^{-3} mg/ℓ (estimated)	Lyman et al., 1982; Hansch and Leo, 1985
Log K_{ow} at pH 7 and 25°C:	7.54	Hansch and Leo, 1985
Log K_{oc}:	5.48 (estimated)	Lyman et al., 1982

Hexachlorophene, being a weak acid, forms salts with alkalis. When heated to achieve decomposition, the compound emits highly toxic fumes (Sax, 1984). Incomplete combustion of the compound may produce haloacids and phosgene. High temperature incineration of hexachlorophene produces hydrochloric acid (OHM TADS data base, 1984, on-line).

1.3. PRODUCTION DATA

The TSCA inventory of chemical production data updated in 1983 (on-line) lists Givaudan Corp, Clifton, NJ as the only manufacturer of hexachlorophene in the United States. It also lists ICD Group, Inc., New York, NY as an importer of this chemical. The reported annual production volume by Givaudan Corp. was 0.1-1.0 million pounds. This is consistent with USITC (1984), which reported Giraudan Corp. as the only manufacturer of hexachlorophene in the United States in 1983. The Directory of Chemical Producers (SRI, 1985) does not list Giraudan Corp. as the U.S. manufacturer of this chemical as of January, 1985 although it listed this company as the sole U.S. manufacturer of hexachlorophene until January, 1984 (SRI, 1984). The Farm Chemicals Handbook (1981) lists Kalo Labs, Inc., Kansas City, MO as the U.S. manufacturer of hexachlorophene. Hexachlorophene is manufactured by the condensation of 2,4,5-trichlorophenol with formaldehyde in the presence of concentrated sulfuric acid (Hawley, 1981). Since the starting material for hexachlorophene production (2,4,5-trichlorophenol) is likely to contain 2,3,7,8-TCDD, the finished product may also contain 2,3,7,8-TCDD as an impurity. Because of additional purification, the level of 2,3,7,8-TCDD in hexachlorophene has been reported to be $\leq$0.03 µg/g (Rappe et al., 1979). The concentration of 2,3,7,8-TCDD in still bottoms and in filter cakes during its manufacturing processes may be much higher. The disposal

of these waste materials and the subsequent widespread contamination of soil with 2,3,7,8-TCDD in the eastern part of Missouri has been described in detail by Powell (1984).

1.4. USE DATA

Before its use was restricted on September 27, 1972, by the U.S. Food and Drug Administration, hexachlorophene was widely used in cosmetic and toilet preparations as an antimicrobial agent. In the past, hexachlorophene had been used in cosmetic preparations such as liquid soap, talcum powder, shampoo and toothpaste (Garratt et al., 1978). It was also used in consumer products for acne and scalp conditions. At least one soap prescribed by physicians for douching to control certain vaginal infections contained hexachlorophene (Singmaster, 1981). After 1972, hexachlorophene use in drug and cosmetic products was restricted to levels $\leq$0.1%. It was also approved by the Food and Drug Administration for surgical scrubbing and handwashing in cases of outbreaks of certain infection. The monosodium salt of hexachlorophene is used in preparations to control fungus on cottonseed, tomatoes, peppers and cucumbers (IARC, 1979; Singmaster, 1981).

1.5. SUMMARY

Although the use of hexachlorophene in consumer products has been extensive in the past, little experimental data on its physical and chemical properties are available in the open literature. It is an odorless, white powdery solid, practically insoluble in water but soluble in most organic solvents. Being a weak acid, it forms salts with alkalis and, hence, ionizes at higher pH. When heated to achieve decomposition, the compound emits highly toxic fumes. As of January, 1984, Givaudan Corp. was the only manufacturer of this compound in the United States, though it may have stopped production of this chemical in 1985. Hexachlorophene was reported to contain $\leq$0.03 µg/g of highly toxic 2,3,7,8-TCDD (Rappe et al., 1979).

The waste materials generated in still bottoms and in filter cakes during the manufacture of hexachlorophene may contain higher levels of 2,3,7,8-TCDD and disposal of these should be carefully controlled.

Hexachlorophene at higher concentrations (~3%) was used in the past as an antimicrobial agent in cosmetic and toiletry preparations. Presently, its use in drug and cosmetic products is restricted to levels $\leq$0.1%. In certain cases, it is also approved for surgical scrubbing and handwashing in hospitals. The monosodium salt is used in fungicide preparations for certain crops.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. AIR

Pertinent data regarding the fate of hexachlorophene in air could not be located in the available literature as cited in the Appendix. Although vapor pressure data for hexachlorophene are not available, the volatility data for structurally similar compounds suggest that this compound probably has a low vapor pressure. Environmental degradation studies with hexachlorophene-treated tomato leaves, peanut leaves and paper discs (used as control) demonstrate the likelihood that volatilization causes slight but insignificant losses of hexachlorophene from these surfaces (Van Auken and Hulse, 1978a, 1979). Therefore, the concentration of hexachlorophene in the ambient atmosphere is likely to be very low. Commercial production and the use of commercial aerosol deodorants containing hexachlorophene may be the source of this chemical in the atmosphere (Will and Varsel, 1966).

If present in the atmosphere, hexachlorophene is likely to be resistant to significant oxidation and photolysis, the two important routes for the degradation of an organic chemical in the atmosphere. This conclusion is based upon the chemical reactivity of hexachlorophene in water (Section 2.2.). Because of its anticipated low vapor pressure and high K_{oc} (see Section 1.2.), it is speculated that hexachlorophene will exist primarily in the particle-sorbed state in the atmosphere. Dry deposition is expected to be the primary physical removal process for this chemical from the atmosphere since the low aqueous solubility will prevent significant removal through wet deposition.

2.2. WATER

The absorption maximum for hexachlorophene in aqueous solution at pH 7 and 8 are at 302 and 312 nm, respectively (Garratt et al., 1978; Moore and

Tamat, 1980). Since hexachlorophene absorbs radiation from sunlight (wavelength >290 nm), it may appear to be photoreactive, depending upon the environment. The photolysis of hexachlorophene solutions both in water and in methanol at wavelengths >290 nm was studied by Moore and Tamat (1980). Photolysis did not involve dissociation of chlorine from the parent compound in either methanol or aqueous solution; however, it shows very slow rates of oxygen uptake upon irradiation. In other words, photolysis of hexachlorophene solutions, in the presence of air with light of wavelength >290 nm, may result in slow degradation of the compound. The photolysis of hexachlorophene in ethanol solution for 5 hours with light of wavelength >260 nm (450 w medium pressure Hanovia mercury lamp) produced 44% unaltered compound, 17% 2,2'-dihydroxy-3,3'5,6,6'-pentachlorodiphenylmethane, 16% 2,2'-dihydroxy-3,5,5',6,6'-pentachlorodiphenylmethane, 2-3% 2,2'-dihydroxy-3,3',6,6'-tetrachlorodiphenylmethane, 2-3% 2,2'-dihydroxy-3,5',6,6'-tetrachlorodiphenylmethane and 18% several other unidentified products. It was speculated that the reactions proceeded by homolytic cleavage of chlorine followed by radical abstraction of hydrogen from the solvent to yield dechlorinated phenol and hydrochloric acid. Although slower, irradiation of hexachlorophene at wavelength >290 nm paralleled the reaction (in terms of products) at wavelength >260 nm, no estimate for the rate of product formation at wavelength >290 nm was given (Shaffer et al., 1971). The photolysis of hexachlorophene applied to tomato leaves and peanut leaves in a study using high intensity fluorescent lamps and incandescent bulbs was reported by Van Auken and Hulse (1978a, 1979). Photodecomposition was 32% from peanut leaves following 114 days of irradiation and 10.5% from tomato leaves following 70 days of irradiation. These investigators found evidence of 13

photolysis products, two of which were identified as 2,2'-dihydroxy-3,5',6,6'-tetrachlorodiphenylmethane and 2,2'-dihydroxy,3,5,5',6,6'-pentachlorodiphenylmethane. The 11 other products remained unidentified.

In the absence of any data on photolysis under environmental conditions, it is difficult to assess the fate of hexachlorophene in natural aquatic media when exposed to sunlight. In aquatic media, where the abstraction of hydrogen from the solvent may not be possible, dechlorination reactions necessary for the formation of bisphenols may not proceed. Therefore, in the absence of hydrogen donating substrate, the photolysis of hexachlorophene in most natural waters may not be significant. The same conclusion was also reached by Sanborn (1974).

In shake-flask experiments, Silberman (1975) studied the fate of hexachlorophene with acclimated microorganisms. Activated sludge, acclimated to hexachlorophene showed a 58% removal of the compound from the aqueous phase in 15 days. The initial concentration of hexachlorophene was 15 mg/ℓ. The primary removal mechanism, however, was adsorption onto the microorganisms and not biodegradation. A small amount of hexachlorophene biodegraded, but the rate of degradation was not reported. Lee and Ryan (1978) studied the microbial degradation of hexachlorophene in sediments from an estuarine river (Skidaway River) near Savannah, GA. The rate of biodegradation of hexachlorophene in the sediment was slow, and the estimated order rate constant was 2.4×10^{-3} day^{-1} at 22°C. The estimated $t_{1/2}$ of biodegradation for hexachlorophene in sediment at 22°C was 290 days. Decreases in water temperatures caused significant decreases in degradation rates in the winter for a few chlorinated compounds. The degradation of the chlorinated compound was faster in sediments than in water.

The fate of selected pesticides including hexachlorophene in a model aquatic ecosystem was studied by Sanborn (1974), who estimated the BCF for hexachlorophene in algae, Oedogonium cardiacum, mosquito fish, Gambusia affinis, and snail, Physa sp., as 1500, 278 and 970, respectively.

Pertinent data regarding the hydrolysis of hexachlorophene in aquatic media could not be located in the available literature as cited in the Appendix. Like other polychlorinated phenols, however, hexachlorophene is not likely to undergo significant hydrolysis (Sanborn, 1974).

Pertinent data regarding the removal of hexachlorophene from water by physical processes could not be located in the available literature as cited in the Appendix. Further, no data regarding the water solubility or the vapor pressure of hexachlorophene were available to estimate Henry's law constant, and thereby qualitatively predict the volatility of hexachlorophene from water. Nevertheless, data regarding the low volatility loss of hexachlorophene from plant leaves during photodegradation studies (Van Auken and Hulse, 1978a, 1979) suggest that this compound will not volatilize significantly from water.

From its reasonably high estimated K_{oc} value (see Section 1.2.), it is speculated that most hexachlorophene in water will be associated with the suspended particulates and sediments in the water. This is consistent with the observation that 33% of hexachlorophene was removed during the flocculation step and 34% during the filtration step of a water treatment process (Buhler et al., 1973). Sims and Pfaender (1975) also found that hexachlorophene levels in the sediment were generally higher than in the water in Cape Fear River basin, NC.

2.3. SOIL

The fate of hexachlorophene in soil has not been studied comprehensively; however, based on its fate in water it is not likely to undergo significant hydrolysis, photolysis or oxidation in soil. The expected higher concentration of microorganisms in soil may cause the biodegradation of hexachlorophene in acclimated soils to be slightly faster than in water. Volatilization from soil may not be significant removal process for hexachlorophene (see Section 2.2.).

The movement of hexachlorophene in soils was studied by Helling et al. (1974) using soil TLC. With Hagerstown silty clay loam, the R_f value for hexachlorophene was only 0.01. Therefore, hexachlorophene is expected to remain almost immobile in most soils. This compound is, therefore, expected to be transported to surface waters by soil washout during heavy rainfalls. The possibility of this compound leaching into groundwater will depend on its biodegradability in soil. Since the mobility of hexachlorophene in soil is very low (Helling et al., 1974), even a slow biodegradation may result in its decomposition in soil before it has a chance to migrate into groundwater. Soil biodegradation studies for hexachlorophene could not be located in the available literature as cited in the Appendix.

2.4. SUMMARY

Pertinent data regarding the fate of hexachlorophene in the atmosphere could not be located in the available literature as cited in the Appendix. The physico-chemical properties of hexachlorophene suggest that it will be present in a particulate sorbed state in the atmosphere. Dry deposition is likely to be an important physical removal mechanism from the atmosphere. In the absence of any documented mechanism for the removal of significant amounts of hexachlorophene, this chemical is likely to persist in the

atmosphere. In water, insignificant amounts of hexachlorophene are expected to be degraded by hydrolysis, photolysis, or biodegradation (Moore and Tamat, 1980; Shaffer et al., 1971; Van Auken and Hulse, 1978a, 1979; Silberman, 1975; Lee and Ryan, 1978). The BCF of hexachlorophene in mosquito fish, Gambusia affinis, was 278 (Sanborn, 1974). Therefore, significant bioconcentration of this chemical in edible aquatic organisms is not likely. The compound may not significantly volatilize from water, but will be associated with the suspended particulates and sediments in water (Buhler et al., 1973; Sims and Pfaender, 1975), and is expected, therefore, to persist in water. According to the only available study about the fate of this compound in soil, hexachlorophene remains immobile in most soils (Helling et al., 1974). Based on its fate in water, significant photolysis, hydrolysis or evaporation of hexachlorophene in soil is unlikely. Whether biodegradation of hexachlorophene in soil will be fast enough to prevent its leaching into groundwater is not known. As in water, hexachlorophene is likely to persist in soils.

3. EXPOSURE

3.1. AIR

Pertinent data regarding the level of hexachlorophene in the atmosphere could not be located in the available literature as cited in the Appendix.

3.2. WATER

Sims and Phaender (1975) reported hexachlorophene concentrations in the North and South Buffalo Creeks in Greensboro, NC. A sewage treatment plant that treats both residential and industrial wastewater is located on each creek. The authors reported finding hexachlorophene concentrations of 4-24.8 ppb upstream of the two treatment plants and 16.4-44.3 ppb downstream. Further downstream, near the confluence with the Haw River, the concentration of hexachlorophene decreased to a level of 3.2-14.8 ppb, as a result of dilution over distance. Hexachlorophene levels in sediment were generally higher than in water and varied from 9.3-377 ppb.

The level of hexachlorophene in sewage influent and effluent water samples collected from three Oregon cities (Corvallis, Eugene and Salem) ranged 20-31 and 6-12 ppb, respectively (Buhler et al., 1973). This represented a 60-70% removal of hexachlorophene in the sewage treatment plants. The concentration of hexachlorophene in the William River, upstream from the city of Corvallis fell within the 0.01-0.1 ppb range.

Hexachlorophene has been detected in two finished drinking water samples in the United States (Shackleford and Keith, 1976); however, neither the sources nor the levels of hexachlorophene in these waters have been reported. Hexachlorophene was detected at a concentration of 0.01 ppb in the finished drinking water from the Corvallis Taylor water treatment plant (Buhler et al., 1973).

3.3. FOOD AND OTHER MEDIA

Before the Food and Drug Administration restricted the use of hexachlorophene on September 22, 1972 in response to an outbreak of accidental hexachlorophene poisoning in France (Martin-Bouyer et al., 1982), several consumer products contained hexachlorophene.

In the past, preparations containing hexachlorophene were used to disinfect the nipples of nursing mothers. Six samples of human milk taken from nursing mothers with unknown patterns of use (before discontinuing use in 1972) contained <2-9.5 ppb hexachlorophene, with a mean of 5.7±2.9 (standard deviation). Two years later, only one of the five samples contained hexachlorophene at a concentration of 8.3 ppb. No detectable level of hexachlorophene was found in 20 samples of commercial cows milk (West et al., 1975).

Human tissue levels of hexachlorophene resulting from using products containing this chemical were studied by several authors. In a study to determine the blood level among users of body and hand soaps containing 1-3% hexachlorophene, the concentration of hexachlorophene ranged from 0.005-0.38 µg/ℓ compared with the control blood level of 0.02 µg/mℓ. Hexachlorophene levels in blood resulting from prolonged use of (0.3-16 years) a soap containing 0.75% hexachlorophene ranged from 0.02-0.14 µg/mℓ with a mean of 0.07±0.04 (standard derivation). Hexachlorophene concentrations in human blood following daily use of mouthwash containing 0.5% hexachlorophene for ~3 weeks ranged from 0.02-0.12 µg/mℓ with a mean of 0.06±0.02 (standard deviation). Human adipose tissue taken from the neck and abdomen of random individuals showed mean hexachlorophene concentrations of 0.01 and 0.04 µg/g of tissue, respectively (Ulsamer et al., 1973). In a similar study with hospital patients using soap, detergent or foam containing

hexachlorophene for a period of up to 8 weeks, the mean blood hexachlorophene levels ranged from 0.06-0.20 μg/mℓ compared to a hexachlorophene level in nonusers of 0.03 μg/mℓ. The follow-up blood samples taken 2-3 years after termination of product use indicated rapid return to the nonusers level (Butcher et al., 1973). Before the discontinuation of its use in 1972, hexachlorophene was widely used as an antibacterial agent to wash infants after birth. To determine possible skin absorption as a result of these washings, blood sample from 50 infants at the time of discharge from the hospital and blood samples from the umbilical cords of the same infants were analyzed (Curley et al., 1971). Hexachlorophene levels in the blood at time of discharge ranged from 0.009-0.646 μg/g with a mean of 0.109 μg/g, and in the umbilical cord, hexachlorophene levels ranged from 0.003-0.182 μg/g with a mean of 0.022 μg/g.

3.4. OCCUPATIONAL LEVEL

A 1974 NIOSH survey established that hexachlorophene exposure occurred primarily in hospitals, sanitariums, convalescent homes, and rest homes that used products containing this chemical (IARC, 1979). Blood hexachlorophene levels in hospital surgical personnel scrubbing with soap and detergents containing 0.25-3% hexachlorophene ranged from 0.07-0.22 μg/g compared with a level of 0.03 μg/g in the control group (Butcher et al., 1973).

3.5. SUMMARY

Pertinent data regarding the atmospheric level of hexachlorophene could not be located in the available literature as cited in the Appendix. Although hexachlorophene has been detected in urban surface water and in surface water downstream from sewage treatment plants at concentrations up to 44.3 ppb (Sims and Pfaender, 1975), only limited studies report the level of hexachlorophene in drinking water. The level of hexachlorophene in the

drinking water in Corvallis, OR was reported to be 0.01 ppb (Buhler et al., 1973). Hexachlorophene has been detected in the milk of nursing mothers at concentrations <2-9.5 ppb. No hexachlorophene has been found in commercial cow milk (West et al., 1975). Hexachlorophene has been detected in the tissues of hospital patients and physicians using products containing hexachlorophene. The blood hexachlorophene levels in hospital surgical personnel ranged from 0.07-0.22 μg/g compared with a level of 0.03 μg/g in the control group (Butcher et al., 1973). Human adipose tissue from the neck and abdomen of random individuals showed mean hexachlorophene levels of 0.01 and 0.04 μg/g of tissue, respectively (Ulsamer et al., 1973).

4. PHARMACOKINETICS

4.1. ABSORPTION

Several studies with hexachlorophene administered orally to rats show only that absorption is rapid but do not indicate the extent to which GI absorption occurs.

In an experiment conducted at IBT Laboratories, Kennedy et al. (1977) found detectable blood levels of radioactivity as early as 0.5 hours in pregnant rats given a single 10 mg/kg gavage dose of [^{14}C-methylene]hexachlorophene in carboxymethylcellulose. Peak blood levels of radioactivity, equivalent to 4.6 ppm hexachlorophene, were obtained 4 hours after treatment. Similar results were obtained in another IBT study in which female rats were sacrificed at 0-12 hours following the last of five consecutive daily gavage doses of unlabeled hexachlorophene in aqueous carboxymethylcellulose (Kennedy et al., 1976a). The peak blood level of hexachlorophene, 1.43 ppm, occurred 4 hours after the last dose in rats treated with 6.5 mg/kg/day. In another IBT experiment in this series, Kennedy et al. (1976a) found no age-related differences in the blood levels of hexachlorophene in female rats given a single gavage dose of 40 mg/kg and sacrificed 4 hours later. Ages tested were 21, 60, 100 and 200 days; there were five rats in each age group.

Bjondahl and Isomaa (1976) treated groups of male Sprague-Dawley rats with single gavage doses of [^{14}C-methylene]hexachlorophene in ethanol and carboxymethylcellulose at 20, 60 and 35 mg/kg in rats of 20, 32 and 85 days of age, respectively. In order to determine levels of radioactivity in plasma and selected tissues, subgroups of 4-5 rats from each group were sacrificed at 6 hours and 1, 4 and 10 days following treatment. In contrast to the findings of Kennedy et al. (1976a), Bjondahl and Isomaa (1976) found

that plasma levels of radioactivity were highest in all age groups at the first sampling and were ~4-10 times higher (0.41% of administered dose/100 mg of plasma) in 20-day-old rats than in 32- or 85-day-old rats (0.10 and 0.04% of administered dose/100 mg of plasma). The higher plasma levels of radioactivity in the 20-day-old rats may reflect greater efficiency of absorption, possibly due in part to a difference in diets, as 20-day-old rats were nursing, but 32- and 85-day-old rats were maintained on standard laboratory ration. It is also possible that mechanisms of elimination of hexachlorophene are not as efficient in 20-day-old rats compared with older rats. By 10 days, 77.54, 76.72 and 91.27% of the administered dose had been recovered in the feces from 20-, 32- and 85-day-old rats, respectively. The differences in fecal recovery were not statistically significant.

The fecal recovery of 76.72-91.27% of an oral dose of hexachlorophene in rats (Bjondahl and Isomaa, 1976) may indicate GI absorption of only a small proportion of an oral dose. Gandolfi and Buhler (1974, 1977), however, determined that biliary excretion and enterohepatic recirculation are extensive (Section 4.4.). Although these authors did not provide experimental data and results, they mentioned unpublished work at their laboratory in which similar blood and tissue distribution patterns following oral and i.p. administration were observed in rats. They concluded that orally administered hexachlorophene "was rapidly and almost completely absorbed."

Since hexachlorophene is used primarily as a topical disinfectant in soaps and detergents and most cases of human toxicity have resulted from dermal exposure, a discussion of dermal absorption is warranted.

Dermal absorption experiments in rats indicate that peak blood levels of radioactivity following application of ^{14}C-hexachlorophene occurred at 6 hours (Kennedy et al., 1977) and 12 hours (Nakaue and Buhler, 1976).

Substantial decreases in blood levels were noted by 24 hours. The age of the rats appeared to have no affect on the rate of dermal absorption (Nakaue and Buhler, 1976; Kennedy et al., 1976a), but significant differences in skin penetration were noted depending on the vehicle. Greatest penetration was achieved with dimethylsulfoxide followed, in descending order, by corn oil, ethanol, and aqueous sodium laurel sulfate (Nakaue and Buhler, 1976).

In species comparison experiments, Chow et al. (1978a) determined that rats, guinea pigs and swine absorbed 76.6, 66.9 and 18% of dermal doses of ^{14}C-hexachlorophene, respectively, based on urinary and fecal recovery. Pigs also absorb hexachlorophene when applied in the dry preparation form (Taylor et al., 1972). Absorption through the skin is enhanced by wounds and lacerations and by subjection to second degree burns (Carroll et al., 1967).

Hexachlorophene is rapidly absorbed through the skin of infant monkeys (Lockhart, 1972) and the skin of human infants (Chilcote et al., 1972, 1977; Anderson et al., 1975; Goutieres and Aicardi, 1977; Tyrala et al., 1977; Gillespie et al., 1974; Kopelman, 1973; Cunningham and Tsoulos, 1972). These and several other studies (Kimbrough, 1973; Powell and Lampert, 1979; Bressler et al., 1977; Anonymous, 1974; Garcia-Bunuel, 1982) indicate that blood levels in infants subjected to routine antiseptic skin care are $\geq$3.0 ppm. Low birth weight or premature infants are more likely to achieve higher blood levels than normal neonates; generally, lower blood levels are common in exposed adults (Calesnick et al., 1975; Bressler et al., 1977; Kimbrough, 1973). Infant skin appears to be more permeable to hexachlorophene (West et al., 1981; Kimbrough, 1976; Powell and Lampert, 1979), particularly if hyperemic or injured (Van Auken and Hulse, 1978b).

Hexachlorophene has been used in feminine hygiene products and obstetrical lubricants (Kimmel et al., 1974). Its absorption through vaginal mucosa has been studied in rats and women. Chow et al. (1978b) applied a dose of 0.87 mg/kg of [^{14}C-methylene]hexachlorophene in corn oil to the vagina of adult Wistar rats, monitored blood concentrations of radioactivity during 24 hours post-treatment and collected feces and urine for 5 days. Blood levels of radioactivity were detectable at 0.5 hours, the first post-treatment sampling time, and peaked at ~2 hours. Less than 10% of the applied radioactivity was recovered from the vagina of rats sacrificed 4 hours after treatment. These data indicate the rapidity and extent to which hexachlorophene is absorbed through the vagina of the rat. After 5 days, recovery from the feces and urine accounted for 72.3 and 3.73% of the administered dose, respectively, or a total of 76.03%. Fecal and urinary recovery of an i.v. dose of the same magnitude accounted for 85.2 and 4.61% (total 89.81%) of the total dose of radioactivity. These data suggest that absorption of hexachlorophene through the vagina of rats is nearly complete.

Kimmel et al. (1974) compared the plasma and tissue levels of radioactivity in rats following oral, dermal or vaginal administration of [^{14}C-methylene]hexachlorophene. The radioactive material was suspended in 1% polysorbate and administered to female Charles River rats at 150 mg/kg on day 10 of gestation. Tissue levels measured 24 hours after treatment indicate that similar uptake occurs following oral or vaginal administration of equivalent doses to pregnant rats (Table 4-1).

Strickland et al. (1983) noted that hexachlorophene is absorbed through the vagina of women during labor, and analyzed maternal and umbilical cord (infant) blood of women examined 2-11 times during labor with a hexachlorophene-containing lubricant. Levels in maternal serum ranged from 0-0.942

TABLE 4-1

Uptake and Distribution of ^{14}C-Hexachlorophene in Rats
24 Hours After Treatment with 150 mg/kg[a]

Tissue	Route of Administration		
	Oral[b]	Vaginal[b]	Dermal[b,c]
Plasma	70.3± 9.3	38.4± 4.7	6.8±3.9
Fetus	5.7± 0.5	4.1± 0.8	4.0±0.8
Placenta	22.4± 2.1	19.8± 3.9	2.9±1.8
Uterus	28.1± 3.1	18.7± 2.2	5.3±2.9
Liver	47.2±20.2	58.7±18.9	11.8±7.0
Kidney	26.1± 7.2	27.3± 6.3	6.5±4.3
Brain	3.7± 1.1	1.9± 0.6	NR

[a]Source: Kimmel et al., 1974

[b]Radioactivity, expressed as ppm hexachlorophene equivalent, mean ± SD

[c]Four of six treated rats had no detectable radioactivity above background in fetus, placenta or uterus

NR = Not reported

ppm, and in infant serum, from 0-0.423 ppm. There appeared to be no correlation between the number of examinations and maternal or infant blood levels. The authors concluded that hexachlorophene was variably absorbed through the vagina.

4.2. DISTRIBUTION AND RETENTION

Chow et al. (1978b) administered i.v. bolus doses of [^{14}C-methylene] hexachlorophene of 0.87 or 3.87 mg/kg in saline to adult female Wistar rats. A semilogarithmic plot of the blood concentrations with time yielded superimposable biphasic curves that fit the conditions of a 2-compartment open model, the first (α) phase of which represents distribution from the circulation to the body tissues.

The distribution of radioactivity following i.v. administration of [^{14}C-methylene]hexachlorophene was studied by whole body autoradiography in a marmoset monkey pregnant 117 days (Brandt et al., 1983). At 24 hours after treatment, heaviest labeling was observed in the liver followed by the blood and highly vascular organs such as the meninges, lungs and placenta, and excretory organs such as the kidney and intestine. Somewhat lower levels of radioactivity were noted in the fetus, and levels in the maternal brain were very low. In a monkey pregnant 119 days and killed for autoradiography 4 days after i.v. treatment, the overall concentration of label was lower substantially, but the relative pattern of distribution was similar to that observed 24 hours after treatment. Levels in the fetus were less than those of corresponding maternal tissues except for the brain, which remained low in both dam and fetus. In early-stage embryos (32-50 days of gestation), a marked tendency of label to accumulate in the neural tube was noted 4 hours after treatment of the dam. The distribution of radioactivity in an 11-day-old marmoset infant 72 hours after treatment was similar to that observed in adult monkeys.

Brandt et al. (1979) performed similar studies in pregnant mice. They administered radiolabeled hexachlorophene in peanut oil by s.c. injection or radiolabeled hexachlorophene in dimethylsulfoxide by i.m. injection. Distribution of radioactivity in mice was similar to that in i.v. treated monkeys except that levels in the liver were very high and much higher than levels in blood. Levels higher than those in blood and lower than those in liver were located in the lungs, pancreas, salivary glands, corpora lutea and adrenal cortex. Levels in the brain were consistently low, while levels in fetal tissues exceeded those of maternal blood. In the early stages of gestation (days 8 and 9) fetal uptake of radioactivity was greatest in those tissues growing most rapidly (e.g., endoderm, ectoderm and somites), especially in neural epithelium. In later stages of gestation, highest concentrations in the fetus were found in the intestinal contents. The fetal liver did not accumulate radioactivity as did the adult liver.

Nakaue and Buhler (1976) applied radiolabeled hexachlorophene dermally to adult, weanling and newborn male Wistar rats and measured the radioactivity in several tissues after 24 hours of exposure. The results, presented in Table 4-2, indicate that in blood, substantially more radioactivity is associated with the plasma than the cells, which is presumably due to the binding of hexachlorophene to plasma proteins. Highest tissue levels were detected in the liver and kidneys, while lowest levels were detected in the brain, fat, muscle and spleen. High levels in the small intestine and its contents probably reflect biliary excretion through the liver.

The percutaneous absorption and tissue distribution of [^{14}C-methylene] hexachlorophene in rats was compared with that in guinea pigs (Chow et al., 1978a). Male animals were treated with 208 µg of chemical and sacrificed 5 days later. Tissue levels were higher in guinea pigs than in rats, but

TABLE 4-2

Tissue Residues of Radioactivity, Expressed as Hexachlorophene Equivalent, in Rats Treated Dermally with [^{14}C-Methylene]hexachlorophene[a]

Tissue	Adult[b,c]	Weanling[b,d]	Newborn[b,e]
Blood cells	7.7± 1.6	16.8± 3.3	1.6± 2.2
Plasma	42.5± 2.0	51.1±11.9	85.5±22.0
Brain	4.7± 1.4	10.3± 2.1	9.1± 0.6
Fat	5.9± 1.6	13.9± 0.1	NR
Heart	12.1± 2.4	20.5± 8.3	20.3± 8.9
Small intestine and contents	194 ±80	163 ±61	76.3±11.9
Kidney	74.9± 1.6	79.8± 3.5	37.4±15.3
Liver	106 ±12	116 ±12	62.5±16.6
Muscle	2.7± 0.4	9.8± 2.7	35.5± 9.6
Spleen	8.8± 1.1	13.1± 6.1	11.6± 8.8

[a]Source: Nakaue and Buhler, 1976

[b]Expressed as ppb hexachlorophene equivalent; mean ± SD

[c]Exposed to 43.2 ng/mm^2 of skin for 24 hours

[d]Exposed to 62.1 ng/mm^2 of skin for 24 hours

[e]Exposed to 206 ng/mm^2 of skin for 24 hours

NR = Not reported

the relative distribution was similar between the two species. Highest levels were located in the livers (199.6 and 117.2 ppb hexachlorophene equivalent in guinea pigs and rats, respectively) followed in descending order by kidney, plasma, whole blood and brain (<10 ppb in both species).

The distribution of [^{14}C-methylene]hexachlorophene was also studied in two male New Zealand white rabbits (Gandolfi and Buhler, 1977). Four days after a 15 mg/kg i.p. dose, highest levels of radioactivity were present in the gall bladder and bile, plasma, liver, kidney and contents of the GI tract. Lowest levels were found in the blood cells and brain. The pattern of distribution of hexachlorophene in the rabbit appears similar to that of the other species studied.

In an IBT study, Kennedy et al. (1977) followed the levels of radioactivity in the maternal blood, placenta and fetus of rats for up to 48 hours following oral or dermal treatment (Table 4-3), and the results of their study indicate that similar concentrations of hexachlorophene in the placenta and fetuses were achieved by either route of administration.

These investigators also measured radioactivity in the milk of lactating rats treated orally with ^{14}C-hexachlorophene in aqueous carboxymethyl cellulose. Levels in the milk reached a maximum (hexachlorophene equivalent ~1.131 ppm) 8 hours after a single 10 mg dose, and levels in milk were substantially less than levels in maternal blood. In another study in rats, dietary levels of 0, 20 and 100 ppm hexachlorophene for 241 days resulted in levels in milk of 0, 0.07 and 0.33 ppm, respectively (Gaines et al., 1973).

4.3. METABOLISM

The metabolism of hexachlorophene has been studied in rats (Gandolfi and Buhler, 1974) and rabbits (Gandolfi and Buhler, 1977). In the rat study, male Wistar rats were bile duct-cannulated and given single 5 or 10 mg/kg

TABLE 4-3

Levels of Radioactivity, Expressed as Hexachlorophene Equivalent in Selected Compartments of Pregnant Rats Following Oral or Dermal Treatment with ^{14}C-Hexachlorophene[a]

Post-Treatment Time (hours)	Maternal Blood[c]	Placenta[c]	Fetus[c]
	Oral[b]		
0.5	1.047	0.676	0.026
1	2.398	0.836	0.036
2	2.507	0.980	0.114
4	5.095	2.564	0.576
8	3.553	2.390	1.282
24	0.983	1.548	2.634
	Dermal[d]		
6	1.334	0.995	0.725
24	0.396	0.596	1.574
48	0.178	0.337	1.676

[a]Source: Kennedy et al., 1977

[b]Treatment: single 10 mg/kg dose in aqueous carboxymethylcellulose

[c]Expressed as ppm hexachlorophene

[d]Treatment: single 8 mg/kg dose in aqueous carboxymethylcellulose

i.p. doses of [^{14}C-methylene]hexachlorophene. Bile and urine were collected for 48 hours, and TLC separation and gas chromatography of the radioactive components led to the identification of two radioactive compounds. About 95% of the radioactivity in the bile was identified as hexachlorophene monoglucuronide; the remainder appeared to be unchanged hexachlorophene and hexachlorophene dimethyl ether. Analysis of the urine revealed that over 90% of the recovered radioactivity was the monoglucuronide conjugate; the remainder was unchanged hexachlorophene.

In an experiment to demonstrate enterohepatic recirculation (Section 4.4.), Gandolfi and Buhler (1974) transferred bile collected from one i.p. treated rat to the duodenum of a recipient rat and analyzed the bile produced by the recipient rat. "Almost all" the radioactivity excreted in the bile of the recipient was identified as hexachlorophene monoglucuronide conjugate. Gandolfi (1973) found that in vitro incubation of hexachlorophene with rat liver microsomal systems did not result in glucuronide conjugation or other metabolism of the chemical. Further details of this experiment are not available.

Gandolfi and Buhler (1974) also studied the metabolism of [^{14}C-methylene]hexachlorophene in rabbits. Urine and feces were collected for 4 days and analyzed for radioactive metabolites of hexachlorophene following a single 15 mg/kg i.p. dose to male New Zealand white rabbits. Urinary metabolites consisted of the monoglucuronide (11.7% of the dose), unchanged parent compound (6.0% of the dose) and other unidentified metabolites (1.6% of the dose). In the feces, 98% of the radioactivity (37.2% of the dose) was present as unconjugated hexachlorophene, 0.8% of the dose as conjugated hexachlorophene and 9.6% of the dose as unidentified material. In another

part of this experiment, expired air was collected from rabbits treated with a 10 mg/kg i.p. dose of ^{14}C-hexachlorphene. No $^{14}CO_2$ or other radioactive volatiles were recovered from expired air.

Gandolfi et al. (1972) reported that the diglucuronide of hexachlorophene was identified as a urinary metabolite in rats and rabbits; however, in more recent studies, Gandolfi (1973) and Gandolfi and Buhler (1974) make no mention of a diglucuronide of hexachlorophene.

4.4. EXCRETION

Studies of the excretion of hexachlorophene and its metabolites are most extensive in rats. Gandolfi and Buhler (1974) administered 5 or 10 mg/kg ^{14}C-hexachlorophene by i.p. injection to rats. Over a 2-3 day period, biliary recovery accounted for ~30 and 45% of the 5 or 10 mg/kg doses of administered radioactivity, respectively. The authors noted that these rates of recovery were substantially less than the 65-75% of a 5 mg/kg dose recovered from the feces of rats treated by i.p. injection, and they hypothesized that extrabiliary gastric or intestinal excretion occurs.

To study the phenomenon of enterohepatic recirculation, Gandolfi and Buhler (1974) administered a 5 mg/kg i.p. dose of ^{14}C-hexachlorophene to a bile duct-cannulated rat whose cannula drained into the duodenum of a second similar sized rat. Bile collected from the recipient rat for 4 days was analyzed and found to contain ~30% of the theoretical dose received from the bile of the donor rat. This experiment demonstrates that enterohepatic recirculation was substantial. A similar conclusion was reached by Edelson and McMullen (1976), who collected bile from ^{14}C-hexachlorophene-treated rats and administered that bile by gavage to nine rats. Radioactivity was isolated from the bile of the recipient rats.

Chow et al. (1978b) studied the excretion of radioactivity in rats following a 0.87 mg/kg i.v. dose ^{14}C-hexachlorophene. Over a 5-day collection period, fecal and urinary excretion accounted for 85.2 and 4.61% of the dose, respectively. The blood time-course concentration curves prescribe a 2-compartment open model with an elimination phase $t_{1/2}$ for radioactivity of 7.97-8.82 hours. Powell and Lampert (1979) reported a biological $t_{1/2}$ of 18 hours (species not reported).

Edelson and McMullen (1976) administered doses of 0.55 or 5.0 mg/kg ^{14}C-hexachlorophene in the portal vein of rats and recorded the level of radioactivity in the bile for the following 24 hours. A biphasic decline in the level of radioactivity was observed in 0.55 mg/kg rats, but the level of radioactivity in 5.0 mg/kg rats remained constant at a substantially higher level for the first 8 hours after treatment. The authors concluded that the biliary excretory mechanisms had been saturated at the higher dose, and that biliary excretion is the rate limiting factor in the elimination of hexachlorophene from the body.

Other routes of excretion can increase in activity as biliary excretion reaches saturation, as shown by Gandolfi and Buhler (1974). These authors administered single 5 mg/kg doses of ^{14}C-hexachlorophene by i.p. injection to bile duct-ligated rats and measured the radioactivity excreted in the urine and feces over a 5-day period. With the bile duct ligated, urinary excretion accounted for 55% and fecal excretion for 13% of the administered dose of radioactivity. These findings support an extrabiliary GI route of excretion for hexachlorophene and confirm that urinary excretion can increase markedly when biliary excretion is hindered.

Gandolfi and Buhler (1977) also investigated the excretion of radioactivity by rabbits treated with ^{14}C-hexachlorophene. Fecal and urinary excretion were measured for 3.5-5 days after i.p. doses of 10 or 15 mg/kg and accounted for 47.7-51.7 and 20.8-24.9%, respectively, of the dose of radioactivity. The authors suggested that the molecular weight of the hexachlorophene conjugate is sufficiently high to be preferentially excreted in the bile rather than by the kidneys.

Chung et al. (1973) determined a plasma $t_{1/2}$ of 4.5 hours for ^{14}C-hexachlorophene. The mice were treated with 6 mg/kg by s.c. administration. Tyrala et al. (1977) determined the concentrations of hexachlorophene in the blood of six infants bathed repeatedly with hexachlorophene-containing disinfectant soaps. The $t_{1/2}$ of hexachlorophene in blood ranged from 6.1-44.2 hours. There was no correlation with body weight, age, length of gestation or "degree of clinical illness."

4.5. SUMMARY

The absorption or uptake of hexachlorophene from the GI tract has been widely investigated and found to be rapid and extensive (Kennedy et al., 1977; Bjondahl and Isomaa, 1976; Gandolfi and Buhler, 1974, 1977). Dermal absorption appears to be somewhat slower but nearly as extensive as oral administration, at least in rats and guinea pigs, as measured by recovery in excretion (Kennedy et al., 1977; Nakaue and Buhler, 1976; Chow et al., 1978a). Absorption occurs through the skin of humans, particularly infants, and has led to cases of intoxication in infants (Chilcote et al., 1972, 1977; Anderson et al., 1975; Goutieres and Aicardi, 1977; Tyrala et al., 1977; Gillespie et al., 1974; Kopelman, 1973; Cunningham and Tsoulos, 1972). Absorption through the vaginal mucosa appears to be similar in rate and extent to GI absorption (Kimmel et al., 1974; Chow et al., 1978b).

Following absorption, levels of radioactivity associated with ^{14}C-hexachlorophene were located in the blood and other highly vascular organs, liver, kidney, placenta and the GI tract and its contents (Brandt et al., 1979, 1983; Nakaue and Buhler, 1976; Chow et al., 1978a). Plasma-protein binding results in substantially greater association with the plasma than with erythrocytes (Nakaue and Buhler, 1976). The pattern of distribution observed was similar in all species (monkeys, rats, rabbits, guinea pigs) studied. Relatively lower levels were located in the brain.

Hexachlorophene or its metabolites were shown to readily cross the placenta and locate in the fetus (Brandt et al., 1979, 1983; Kimmel et al., 1974; Kennedy et al., 1977). Generally, levels in the fetus were lower than those in the maternal blood and tissues. Exposure during early gestation resulted in the location of hexachlorophene in actively proliferating fetal tissues, especially the neural tube (Brandt et al., 1979). Hexachlorophene or its metabolites can also reach the newborn through the mother's milk (Kennedy et al., 1977; Gaines et al., 1973).

The metabolism of hexachlorophene has been studied extensively in rats (Gandolfi and Buhler, 1974) and rabbits (Gandolfi and Buhler, 1977). Hexachlorophene monoglucuronide was found as the major metabolite (>95% of the radioactivity following treatment with ^{14}C-hexachlorophene) in the bile of rats and the urine of rats and rabbits. Most of the remaining radioactivity was identified as parent compound. In rabbits treated by i.p. injection, 98% of the radioactivity excreted in the feces was associated with unaltered hexachlorophene.

In the rat, biliary excretion accounts for 30-45% of the radioactivity excreted following i.p. injection and is considered to be the rate-limiting step in the elimination of hexachlorophene and its metabolites. In intact

rats, fecal excretion typically accounts for 65-75% of an i.p. dose, and it has been shown that GI secretion of hexachlorophene metabolites may occur. In the rat, a substantial amount of enterohepatic recirculation occurs (Gandolfi and Buhler, 1974; Edelson and McMullen, 1976).

Urinary excretion is a considerably less important pathway of elimination. In rats treated intravenously, 85.2 and 4.61% of the administered dose of radioactivity was recovered from the bile and urine, respectively (Chow et al., 1978a). The urinary route appears to be somewhat more important in rabbits, however, as 47.7-51.7 and 20.8-24.9% of the radioactivity from i.p. administered ^{14}C-hexachlorophene was recovered from feces and urine, respectively (Gandolfi and Buhler, 1977). Ligation of the bile duct in rats increases urinary excretion to 55% of the administered dose of radioactivity (Gandolfi and Buhler, 1974).

The estimated $t_{1/2}$ of radioactivity in plasma associated with ^{14}C-hexachlorophene in rats was 7.97-8.82 hours (Chow et al., 1978b) and in mice, 4.5 hours (Chung et al., 1973). In human infants, the estimated $t_{1/2}$ of hexachlorophene in the blood was 6.1-44.2 hours (Tyrala et al., 1977).

5. EFFECTS

5.1. CARCINOGENICITY

An NCI (1978) bioassay was performed in Fischer 344 rats using dietary levels of 0, 17, 50 or 150 ppm hexachlorophene of ≥98% purity. There were 24 male and 24 female rats at each dietary level. Feeding continued for 105-106 weeks (females) or 106 weeks (males), at which time survivors were sacrificed. Gross and microscopic examinations were conducted on all rats that died during the experiment and those sacrificed at termination. Treatment had no effect on clinical signs, body weight or mortality. A respiratory infection occurred in control and treated rats at week 24, but recovery without treatment appeared to be complete within 4 weeks. In male rats, interstitial cell tumors of the testes were the most frequently observed neoplasm, but the incidence in treated rats was not significantly greater than in control rats. In female rats, granulocytic leukemias predominated, but the incidence was comparable in control and treated rats and was not treatment-related.

The carcinogenicity of hexachlorophene ("especially pure") was also investigated in Sprague-Dawley rats (Rudali and Assa, 1978). In this experiment, the control and hexachlorophene-treated groups, each containing 15 male rats at 6 months of age, were fed diets deficient in protein and vitamins. The investigators stated that they have routinely used this diet for several years to enhance the induction of liver cancer by exposure to azo compounds. One group of rats was maintained as controls and the other group received a diet to which 50 ppm hexachlorophene had been added. Treatment continued throughout the lifespan of the rats, but appeared to have no effect on longevity, body weight gains or organ weights. No tumors occurred, with the exception of a pituitary adenoma in one treated rat, which was not associated with exposure to hexachlorophene.

Rudali and Assa (1978) also tested hexachlorophene for carcinogenicity in two strains of mice. Controls consisted of 25 male and 25 female C57Bl and 37 male and 38 female XVII/G mice. Diets containing 150 ppm were fed to 35 male and 33 female C57Bl and 38 male and 40 female XVII/G mice from 25 days of age throughout their lifespan. The C57Bl strain has been bred to spontaneously develop leukemias (~1%), reticulosarcoma (10-15%) and liver tumors (1-3%). XVII/G mice spontaneously develop single but not multiple lung adenomas (~70%). Treatment appeared to have no effect on survival. Generally, the only tumors that developed were those common to the specific strain of mice and these occurred with comparable frequency in treated and controls. Multiple lung adenomas were not observed in XVII/G mice.

In an experiment with nursing XVII/G mice, the offspring of 7 mice were nursed by dams treated (route unspecified) with 0.5 mg of hexachlorophene (Rudali and Assa, 1978). Untreated and positive treated (methylcholanthrene) controls were maintained, and nursing was continued for 20 days. Multiple pulmonary adenomas were induced only in positive control mice. In other experiments in this series, the offspring of XVII/G mice were treated with hexachlorophene subcutaneously at 0.05, 0.05 and 0.1 mg on days 1, 2 and 8 and were observed for lifespan. In another experiment, C57Bl females mated to C3H males were injected (route unspecified) with hexachlorophene at 0.5 mg on gestation days 16 and 18. In these experiments, treatment of neonates or of pregnant dams resulted in no evidence that hexachlorophene was carcinogenic in these specially developed strains of mice.

As reviewed briefly by Mahfouz (1982), dietary concentrations of hexachlorophene $\leq$100 ppm (highest dose tested) were not carcinogenic to rats treated for 2 years (IRDC, 1980a) or to mice treated for 21 months (IRDC, 1980b).

The carcinogenicity of hexachlorophene was also studied in the mouse skin bioassay (Stenback, 1975). In the first study, hexachlorophene was applied twice weekly to the skin of groups of 50 female Swill mice, starting at 8 weeks of age and continuing for lifespan. Treatment was with 0.02 mℓ of 5, 25 or 50% concentration in acetone. In the second experiment, treatment started at 7 weeks, consisted of twice-weekly application of 1% hexachlorophene in acetone for lifetime (Stenback, 1977). Hexachlorophene was negative for carcinogenicity in both of these mouse skin-painting studies. In the first study, necrosis and ulceration of the skin occurred at the treatment site. Neurological symptoms developed and mortality had reached 22% by 2 weeks. The incidence, severity and time-to-effect were similar in all treated groups and no dose-related response was indicated. In the second experiment, local skin irritation was observed but treatment had no effect on survival or body weights and no neurological signs were noted.

Stenback (1977) also applied hexachlorophene at 5, 25 or 50% in acetone to the interior of the ears of 4-6 New Zealand White rabbits for lifespan. Local irritation occurred that progressed to hyperplasia. Carcinogenicity was not demonstrated and other signs of toxicity were not observed.

5.2. MUTAGENICITY

Hexachlorophene has been tested for mutagenicity in the reverse mutation assay in Salmonella typhimurium (Haworth et al., 1983; Arnold et al., 1975; Gocke et al., 1981; Dymin et al., 1984), the chromosomal aberration test in rat bone marrow cells (Dymin et al., 1984) and in human lymphocytes (Vig, 1972), the micronucleus test in mouse bone marrow cells (Gocke et al., 1981; Sylianco, 1978), the sister chromatid exchange test in human lymphoid cells (Sobti et al., 1983), the dominant lethal test in male mice (an IBT study:

Kennedy et al., 1975a; Arnold et al., 1975) and the sex-linked recessive test in Drosophila melanogaster (Basc test) (Gocke et al., 1981) (Table 5-1). All tests were uniformly negative with the exception of two experiments in Eastern bloc countries: Dymin et al. (1984) observed a positive response in S. typhimurium (strain not specified) without metabolic activation (S-9) but negative in the presence of S9 and Syllanco (1978) noted the formation of micronucleated polychromatic erythrocytes in tissue culture of mouse bone marrow cells. Adding vitamin E to the incubation medium appeared to reduce micronucleus formation. The data were not reported for either of these studies; therefore, the authors' conclusions cannot be verified.

5.3. TERATOGENICITY

A number of investigators (Gaines et al., 1973; Oakley and Shepard, 1972; Kennedy et al., 1975b, 1976b; Haley et al., 1973; Thorpe, 1967; Dymin et al., 1984; IRDC, 1979) have studied the teratogenicity of orally-administered hexachlorophene in rats (Table 5-2). In one study no adverse fetal effects or effects on fertility were noted at a dietary level of 1000 ppm or a gavage dose of 100 mg/kg (Thorpe, 1967). In most studies, effects on the dams were noted at $\geq$20 mg/kg/day. Gaines et al. (1973) noted effects on fertility at 20 mg/kg/day; at 30 mg/kg/day, weight loss and neurological signs were noted (Kennedy et al., 1975b, 1976b; Haley et al., 1973). Maternal deaths were noted at 100 mg/kg given once on day 8 of gestation (Thorpe, 1967). Oakley and Shepard (1972) observed neurological signs in rats fed a diet containing 500 ppm hexachlorophene on gestation day 7 or 8. Assuming rats eat food in amounts equivalent to 5% of their body weight/day (U.S. EPA, 1980), an equivalent dose of 25 mg/kg is calculated. These authors also noted that fetuses of these dams were small and 3 (6.8%) had cleft palate ($p<0.05$). In a gavage study, 30 mg/kg on days 6-15 of gestation resulted in reduced fetal body weights and a low but not statistically

TABLE 5-1

Mutagenicity and Genotoxicity of Hexachlorophene

Assay	Indicator/Organism	Compound and/or Purity	Application	Concentration or Dose	Activation System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537	97%	plate incorporation	0-3 µg/plate	±S-9	-	In DMSO; negative in all strains	Haworth et al., 1983
	S. typhimurium G46	NR	host-mediated in male rats	100 or 200 ppm in diet for 90 days	NA	-	3-Hour residue time in rats	Arnold et al., 1975
	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	NR	plate incorporation	up to 3600 µg/plate	±S-9	-	Tested in two different media	Gocke et al., 1981
	S. typhimurium NOS	NR	liquid incubation	10-100 µg/mL	±S-9	+	No data provided by investigators	Dymin et al., 1984
Chromosomal aberration test	rat bone marrow cells	NR	inhalation exposure	0.2, 1.67 or 33.5 mg/m³	NA	-	Experimental protocol insufficiently reported	Dymin et al., 1984
	human lymphocytes	NR	tissue culture	1-200 mg/L for 6-21 hours	NA	-	Dose- and time-dependent depression of mitosis was observed	Vig, 1972
Micronucleus test for chromosomal damage	NMRI mice	NR	treated i.p. at 0 and 24 hours	0-8.0 mg/kg/dose	NR	-	2 male and 2 female mice used at each dose level	Gocke et al., 1981
	mouse bone marrow cells	NR	tissue culture	NR	NA	+	No data provided. Abstract only.	Sylianco, 1978
Sister chromatid exchange	human lymphoid LAZ-007 cells	NR	tissue culture	10^{-4} to 10^{-6} M	±S9	-	In DMSO	Sobti et al., 1983
Dominant lethal	male mice	NR	i.p. injection	2.5 or 5.0 mg/kg single dose	NA	-	12 Males/group; mating continued for 8 weeks post-injection (study conducted at IBT Laboratories	Kennedy et al., 1975a; Arnold et al., 1975
Sex-linked recessive lethal (basc test)	D. melanogaster	NR	adult feeding method	0.5 mM	NA	-	In 2% alcohol or 2% cremophor	Gocke et al., 1981

TABLE 5-2

Teratogenicity and Fetotoxicity of Orally Administered Hexachlorophene

Vehicle	Species/Strain (number)	Dosage Level and Duration of Treatment	Observation Day	Fetal Response	Maternal Response	Reference
Peanut oil (gavage)	rat/Sherman (8-10)	0, 1, 5, 10 or 20 mg/kg on days 7-15 of gestation	21 days post-partum	all pups appeared normal, no still-births were noted	20 mg/kg: 2/9 failed to litter, 1/9 delivered 1 pup that died shortly after birth	Gaines et al., 1973
Diet	rat/NR (4)	100 ppm "majority of pregnancy" (at least days 7-19 of gestation)	20 (gestation)	54 normal fetuses	Dams remained asymptomatic	Oakley and Shepard, 1972
Diet	rat/NR (4)	500 ppm on days 7 or 8-20	20 (gestation)	44 small fetuses, 3 (6.8%) with cleft palate ($p<0.05$)	Hindlimb paresis, partial anorexia	Oakley and Shepard, 1972
1% Aqueous methyl-cellulose (gavage)	rat/Charles River (36-50)	0, 15 or 30 mg/kg/day on days 6-15 of gestation	20 (gestation)	30 mg/kg: reduced fetal body weights ($p<0.01$); low but not statistically different incidence of stunting, micro- or anophthalmia and angulated ribs; 0, 15 mg/kg: no effects	30 mg/kg: reduced rate of body weight gain; no effects on reproduction parameters at any dose level	Kennedy et al., 1975b*
1% Aqueous methyl-cellulose (gelatin capsule)	rabbit/New Zealand (9-52)	0.3 or 6 mg/kg/day on days 6-18 of gestation	29 (gestation)	6 mg/kg/day: small but not statistically significant increase in incidence of acrania and minor skeletal malformations 0 or 3 mg/kg: no effects	6 mg/kg: reduced rate of body weight gain, increased resorptions due to total resorptions of 2 litters no effects	Kennedy et al., 1975b*
Diet	rat/Wistar (3-4)	0, 500, 1000 ppm throughout pregnancy	20 (gestation)	no adverse effects reported on fetus	no adverse effects reported on fertility	Thorpe, 1967
Diet	rat/NR (NR)	60 ppm on unspecified days of gestation	20 (gestation)	no adverse effects on fetus	NR	IRDC, 1979
1% Aqueous Lissapol-Dispersol OG (gavage)	rat/Wistar (5-6)	0, 50 or 100 mg/kg on day 8 of gestation	20 (gestation)	no adverse effects reported	100 mg/kg: 2 females died within 1 week of treatment; no effects on fertility	Thorpe, 1967

TABLE 5-2 (cont.)

Vehicle	Species/Strain (number)	Dosage Level and Duration of Treatment	Observation Day	Fetal Response	Maternal Response	Reference
1% Aqueous methyl-cellulose (gavage)	rat/COBS (20)	0, 15, 30 mg/kg/day from gestation day 15 through-out lactation	21 days post-partum	≥15 mg/kg: reduced survival at weaning; 30 mg/kg: increased stillborn	30 mg/kg: weight loss, neurological signs and mortality of 2/20	Kennedy et al., 1976b; Haley et al., 1973*
RR (gavage)	rat/NR (NR)	40 mg/kg during entire pregnancy	probably day 21 (gestation)	"no embryotoxic effect"	NR	Dymin et al., 1984

*Study performed at IBT Laboratories

NR = Not reported

significant incidence of stunting, microphthalmia or anophthalmia (Kennedy et al., 1975b). Although the incidence of these malformations was not statistically significant, they are the malformations in rats commonly associated with hexachlorophene (Kimmel et al., 1974). In a gavage study in which treatment started on gestation day 15 and continued through lactation, reduced survival at weaning was observed at 15 mg/kg/day, the lowest level tested (Kennedy et al., 1976b; Haley et al., 1973). It appears that in orally-treated rats, the threshold for teratogenicity was ~25 mg/kg/day (500 ppm in the diet), which was also associated with maternal toxicity (Oakley and Shepard, 1972) and the threshold for fetotoxicity or toxicity to the newborn was ~15 mg/kg/day (Kennedy et al., 1976b; Haley et al., 1973). There may be strain differences in the susceptibility of rats to fetotoxicity or teratogenicity that are due to hexachlorophene exposure.

Orally-treated rabbits appear to be more susceptible than rats to the effects of hexachlorophene during gestation. At 6 mg/kg/day on days 6-18 of gestation, dams had reduced rates of body weight gain and possibly increased fetal resorption (Kennedy et al., 1975b). A small but not statistically significant increase in the incidence of acrania and other minor skeletal malformations was also observed at this dose level.

Kimmel et al. (1972, 1973, 1974) have demonstrated that hexachlorophene is teratogenic to rats when administered by the intravaginal route. Exposure was to ~20, 80 or 300 mg/kg/day on days 7-10 of gestation. At $\geq$80 mg/kg/day there was a significantly increased incidence of hydrocephalus, anophthalmia or microphthalmia. Irritation in the vagina was noted in all treated groups; mortality occurred in the high-dose group.

In other teratology studies, hamsters and mice were treated by s.c. or dermal routes. In hamsters treated subcutaneously, 53 mg/kg administered on day 8 of gestation appeared to be a threshold for teratogenicity, as malfor-

mations were observed in 1.4% of fetuses (Geber, 1977). At 113 mg/kg/day, malformations occurred in 2.6% of fetuses. The nature of the malformations was not discussed. In mice treated s.c. with 12.5-50 mg/kg/day on 6 consecutive days of gestation, increased resorption and fetal mortality were observed but no increased incidence of terata was recorded (Franco et al., 1974; Majumdar et al., 1975). In a Russian dermal study in mice, 30 mg/kg was reported as the threshold for teratogenicity and 15 mg/kg was reported as a threshold for fetotoxicity (Rapoport et al., 1982). No further information was available. In another Russian study (Dymin et al., 1984), inhalation exposure to 33.5 mg/m^3 during 20 days of gestation resulted in decreased numbers of pups delivered and increased neonatal body weights.

Hexachlorophene has been implicated as a human teratogen. Halling (1977, 1979) noted an unusual incidence of minor and major malformations in infants born to nurses working in Swedish hospitals and exposed to hexachlorophene. In a population of 65 neonates born to exposed mothers, six were observed to have serious malformations. In addition, one mother delivered a stillborn infant and six others delivered infants with malformations. Halling (1979) then assembled a control population of 68 births from hospital workers not exposed to hexachlorophene. Only one minor malformation and no major malformations occurred in the control groups. These observations prompted the study of hexachlorophene-exposed workers in four nearby hospitals (Halling, 1979). The case reports of pregnancy outcomes for 460 hexachlorophene-exposed and 233 nonexposed controls from the five hospitals were examined. Major and minor malformations involved 72/460 (15.7%) of the exposed and 8/233 (3.47%) of the controls. Halling (1979) suggested, on the basis of these findings and the known ability of the chemical to cross the placental barrier (see Section 4.3.) that hexachlorophene is teratogenic to humans.

Halling's (1977, 1979) findings prompted the National Board of Health and Welfare in Sweden to study the outcome of pregnancies in Swedish hospital workers (Vainio, 1982). Baltzar et al. (1979a) studied the case histories of ~1500 women who worked in 31 hospitals and gave birth during 1965-1975. In addition, women working in medical occupations who delivered during 1973-1975, the time period of the Halling (1977, 1979) study, were retrospectively examined. The control population for each of these studies was nonmedically employed women who delivered in those hospitals during the study period. The data were corrected for age and purity. Overall, no differences were noted in birth weight, gestation length, perinatal deaths or the incidence of malformations in the study cohort compared with the control population. A slight (but not statistically significant) increase in perinatal deaths and congenital malformations was observed in the years 1973-1975, in the Gothenburg area of Sweden, the area in which Halling (1979) conducted her study. The authors interviewed many of the mothers from the Gothenburg area, but offered no explanation for this apparent clustering of perinatal deaths and congenital malformations. Other investigators (Baltzar et al., 1979b; Janerich, 1979; Kaellen, 1978; Kaellen et al., 1982) have also criticized the Halling (1977) study for faulty design, claiming that Halling (1977) found her exposed cohort by choosing mothers with malformed infants from the "clusters" in the Gothenburg area. According to Vainio (1982) the issue of the teratogenicity of hexachlorophene is unresolved.

5.4. OTHER REPRODUCTIVE EFFECTS

Two- and three-generation reproduction studies have been performed in rats and are summarized in Table 5-3. In one study (Gaines et al., 1973; Gaines and Kimbrough, 1971), reduced survival at weaning and lesions in the

TABLE 5-3

Multigeneration Reproduction Studies in Rats Fed Dietary Hexachlorophene

Strain (number)	Dosage Level	Results	Comments	Reference
Sherman (10/sex)	0, 20, 100 ppm starting at 4-5 weeks of age	0, 20 ppm: no effects on body weight gain, clinical signs, histopathologic lesions of selected organs or fertility; 100 ppm: reduced survival to weaning; status spongiosus of F_{1b} but not F_{2a} offspring	Mating began after 54 days of treatment, continued through 2 generations	Gaines et al., 1973; Gaines and Kimbrough, 1971
Charles River (8 male, 16 female)	0, 12.5, 25.0, 50.0 ppm starting at 21 days of age	No effects on survival, growth pattern, clinical signs, fertility or histopathologic appearance of selected organs including the brain	Mating began at 100 days of age, continued through 3 generations	Kennedy et al., 1975c; Haley et al., 1973*
NR (NR)	20, 60 ppm for 3 generations	No effects at 20 ppm. At 60 ppm: decreased number of corpora lutea and implantations; decreased number of F_{1a} pups surviving until lactation day 4; decreased body weight of pups.	Additional details were not provided in the review	IRDC, 1979

*Conducted at IBT Laboratories

NR = Not reported

brain were noted at a dietary level of 100 ppm in a 2-generation reproduction study in rats. No effects were observed at 20 ppm. No effects were observed at 20 ppm in the IRDC (1979) study; however, decreased numbers of corpora lutea and implantations, decreased F_{1a} pups surviving until lactation day 4 and decreased body weight of pups were observed at 60 ppm. In an IBT study (Kennedy et al., 1975c; Haley et al., 1973) no adverse effects were noted at 50 ppm in the diet.

In a similar IBT study, Kennedy et al. (1976b) administered hexachlorophene in 1% aqueous methylcellulose by gavage at 0, 5 or 10 mg/kg/day to groups of 10 male and 20 female rats. Males were treated beginning at 63 days before mating, females beginning at 14 days before mating until day 14 of gestation (1/2 the group) or until weaning of the resultant litter at 21 days of age. Mating began when the rats were 100 days old. There were no deaths and no effects on clinical signs or rate of body weight gain. In rats killed at 14 days of gestation, no effects were noted on fertility parameters with the exception of a slight increase in resorptions at 10 mg/kg. In dams at 10 mg/kg/day allowed to deliver, a slight but significant decrease in survival at 12 and 21 days was noted. Hexachlorophene has been shown to have an effect on the testes of rats.

Thorpe (1967) administered single oral doses of 25, 75 or 125 mg/kg to groups of 30 male Wistar rats weighing 180-200 g. A control group of 20 rats was treated with vehicle (Lissapol-Dispersol OG) only. Subgroups of four rats were sacrificed on days 1, 2, 5, 12 and 21 for limited histopathological examination. Six rats in the 125 mg/kg groups died, the survivors and those in the 75 mg/kg group developed severe diarrhea. Rats from the 125 mg/kg group killed on the second day showed reduction in testicular and epididymal sperm content and degenerating spermatids. Similar lesions were

detected at 75 mg/kg but not at 25 mg/kg. Considerable testicular regeneration had occurred in 75 and 125 mg/kg rats by day 12. In another part of this experiment, rats treated with 25 mg/kg/day for 5 consecutive days showed no testicular lesions. Livers from rats in the 25 mg/kg/day group had an increased proportion of parenchymal cells in mitosis.

A similar but longer term study in rats and dogs was performed by James et al. (1980). A group of 15 male Sprague-Dawley rats at 35 days of age and a group of four sexually mature beagle dogs were treated with 5 and 3 mg/kg/day, respectively, by gavage for 9 weeks. A group of 15 vehicle (corn oil) treated control rats was maintained. Treatment had no effect on clinical signs, food or water consumption, body weight or serum LH or testosterone concentrations. In both dogs and rats, some statistically significant reductions were found in the populations of specific germinal cells, but the populations of late cell types appeared to be normal. Full testicular recovery in all regards was evident after a 13-week withdrawal period.

Hexachlorophene administered to male rats by inhalation has been shown to decrease the number of spermatozoa in the testis (Dymin et al., 1984). Exposure was to 33.5 mg/m^3 for 1 month (exposure regimen not specified). This effect was not observed at 1.67 mg/m^3.

The effect of exposure to hexachlorophene during the neonatal period upon subsequent sexual maturity has been investigated in rats and hamsters. In hamsters, a critical period for sexual differentiation of the hypothalamus occur within a few days of birth (Alleva, 1973). Groups of 2-25 females were given s.c. injections of hexachlorophene in corn oil at 3 or 6 mg/kg on days 0-12 of age. Groups of 5-31 males were similarly treated on days 0-4. In females, there were no effects on age of puberty, estrus cycle regularity, fertility or body weights; in males, no effects were observed on fertility or body weights, the only parameters evaluated.

In the study with rats, male and female Sprague-Dawley rats were given whole body baths of pHisoHex (containing 3% hexachlorophene) or pHisoDerm (no hexachlorophene) on days 1-8 of age (Gellert et al., 1978). The development of ataxia and tremors in all treated pups by day 9 indicated severe toxicity by dermal exposure. By 14 days of age, 25% of the treated males and 13% of the treated females had died. No effects on puberty, regularity of estrus cycles or fertility were noted in the females. Male fertility was markedly depressed, primarily as the result of inability to ejaculate. Arousal, mounting and intromission activity appeared to be normal. At necropsy, cystic degeneration, fibrosis and architectural disruption of the prostate gland were observed in treated rats. Spermatogenesis appeared to be normal. The authors mentioned that hexachlorophene manufacture uses pentachlorophenol, which contains small quantities of dibenzodioxins as impurities. It is possible that androgenic activity of dermally-absorbed dibenzodioxins in the neonatal period may have caused failure of formation of the CNS tracts responsible for ejaculation.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

5.5.1. Chronic Studies. Few data were located regarding the chronic toxicity of hexachlorophene. In the NCI (1978) bioassay (see Section 5.1.), diets containing 0, 17, 50 or 150 ppm hexachlorophene were fed to groups of 24 male and 24 female Fischer 344 rats for 105-106 weeks. Treatment had no effect on clinical signs, body weight or mortality. In addition, histological examination of the brain revealed no treatment-related lesions suggestive of demyelination, vacuolization or status spongiosus, the lesions of the brain most often associated with hexachlorophene toxicity (Section 5.6.).

In a 2-year feeding study in rats by IRDC (1980a), no effects were observed at 20 ppm. At 100 ppm, rats had reduced body weight gain; food consumption data were not reported. No histological evidence of neurotoxicity was observed at ≤100 ppm; however, as noted by Mahfouz (1982), myelin specific dye was not used. Further details of the IRDC (1980a) study were not provided.

Rudali and Assa (1978) fed a diet containing 50 ppm hexachlorophene to 15 male Sprague-Dawley rats from 6 months of age until death. The base diet was deficient in protein and vitamins and a control group received this base diet without added hexachlorophene. Treatment appeared to have no effect on clinical signs, body weights, survival or organ weights. This experiment was designed as a cancer bioassay, so no other parameters of toxicity were examined.

Rudali and Assa (1978) also fed diets containing 150 ppm hexachlorophene to C57Bl (25 males and 25 females) and XVII/G (37 male and 38 female) mice from 25 days of age to death as a cancer bioassay. There were no clinical signs of toxicity and no effects on survival. Other parameters of toxicity were not evaluated.

In the 21-month carcinogenicity study in mice by IRDC (1980b), hexachlorophene at dietary levels ≤100 ppm was not oncogenic; other indices of toxicity were not reported.

Stenback (1975, 1977) performed lifetime skin-painting bioassays in female Swiss mice with twice-weekly applications of 0.02 mℓ of 1, 5, 25 or 50% hexachlorophene in acetone. Only local irritation was observed with the 1% solution but necrosis and ulceration of the skin accompanied by neurological signs and death were observed with the 5, 25 or 50% solutions.

Assuming rats and mice eat food equivalent in amount to 5 and 13% of their body weight, respectively (U.S. EPA, 1980) the high dietary level of 150 ppm in the NCI (1978) and Rudali and Assa (1978) assays corresponds to 7.5 mg/kg/day in rats and 19.5 mg/kg/day in mice. No adverse effects were noted at these dosages. Adverse effects were noted, however, in subchronic studies at levels substantially lower than these.

5.5.2. **Subchronic Studies.** The literature on subchronic studies of the toxicity of hexachlorophene is extensive. Many of the investigations used high levels for short periods to produce characteristic lesions and, therefore, do not aid in defining thresholds for toxicity.

Several oral studies in rats (Maxwell and LeQuesne, 1979; Matthieu et al., 1974; Towfighi et al., 1973, 1974, 1975; DeJesus and Pleasure, 1973; Powell et al., 1978; Cammer et al., 1975; Kimbrough and Gaines, 1971; Lampert et al., 1973; Benitz et al., 1974; Pleasure et al., 1974; Myers et al., 1982; Hanig et al., 1973, 1977; Kennedy and Gordon, 1976; Kennedy et al., 1976b), mice (Lampert et al., 1973; Tripier et al., 1981a,b) and cats (Hanig et al., 1976) characterize the lesions in the central and peripheral nervous systems. Generally, these studies show that clinical signs start with tremors, motor discoordination, paralysis starting at the rear limbs and loss of righting reflex. Lesions in the brain, called "status spongiosus," include increased brain wet weight (but not dry weight) due to edema, vacuolization of the white matter and increased cerebral-spinal fluid pressure. Peripheral nerves are edematous, myelin sheaths degenerate, neuronal fibers separate, intraneural pressures increase and neuronal blood flow decreases (Myers et al., 1982). Similar lesions and effects were produced in newborn and young rats by dermal exposure (Shuman et al., 1974a), in adult and suckling mice by s.c. injection (Persson et al., 1978), and in

adult and infant monkeys and baboons by s.c. (Galey, 1972) and dermal (Hart, 1971; Tripier et al., 1981a,b) exposure, respectively. Several authors discovered that survivors allowed a recuperation period following treatment showed slow but steady signs of clinical recovery and that lesions in the nervous system became less severe (DeJesus and Pleasure, 1973; Powell et al., 1978; Cammer et al., 1975; Kimbrough and Gaines, 1971; Benitz et al., 1974; Lampert et al., 1973; Kennedy et al., 1976b). High dietary levels ($\geq$200 ppm) in rats were also associated with progressive and severe retinal damage, probably leading to permanent blindness (Towfighi et al., 1975; Rose et al., 1981). These effects are reversible only if treatment is terminated early in the course of the development of this syndrome. Because the studies cited above were performed with high ($\geq$10 mg/kg bw) oral doses or dietary levels ($\geq$200 ppm) that produced frank effects quickly, they are not useful for quantitative risk assessment and are not discussed further.

In addition to the studies mentioned above, a number of oral studies with hexachlorophene that are appropriate for consideration regarding quantitative risk assessment are summarized in Table 5-4. In weanling rats, the minimal dose that appears to be associated with histopathological lesions in the brain is 5-7.7 mg/kg/day (Jones et al., 1974; Nakaue et al., 1973). In weanlings, a threshold for mortality appears to be at 28.9 mg/kg/day and a threshold for transient neurologic effects appears to be at 14.9 mg/kg/day, substantially above the minimum level associated with CNS lesions (Nakaue et al., 1973). The author noted that this hindlimb weakness had disappeared by 2 weeks of treatment, indicating that the rats developed tolerance to the chemical. Reduced growth rate occurred at doses at or higher than those associated with CNS lesions (Jones et al., 1974; Nakaue et al., 1973). No effects were noted on hematological parameters or clinical

TABLE 5-4

Subchronic Oral Toxicity Studies with Hexachlorophene

Species/ Strain	Age	Number, Sex	Dosage Level, Vehicle Duration of Treatment	Transformed Dose (mg/kg/day)	Effects	Reference
Rat/Fischer 344	5 weeks	10-30/sex	0, 50, 100, 200, 400, 600 or 820 ppm in diet for up to 8 weeks	60[a] 40[a] 5[a]	≥600 ppm: increased mortality. ≥400 ppm: reduced rate of body weight gain and clinical signs of neurotoxicity. ≥50 ppm: minimal histopathological lesions of neuronal degeneration	Jones et al., 1974
Rat/Wistar	4 weeks	6/sex/group	0, 12.5, 25, 50, 100, 200 or 400 ppm in diet for 16 weeks	28.9[b] 14.9[b] 7.7[b] 3.7[b] 1.9[b] 0.9[b]	4[illegible] ppm: paralysis and death within 10 days. 200 ppm: transient hind limb weakness 100 ppm: reduced rate of body weight gain, cerebral edema and vacuolization 50 ppm: no effects 25 ppm: no effects 12.5 ppm: no effects	Nakaue et al., 1973
Rat/albino	NR	15/sex/group	0, 20, 65 or 200 ppm in diet for 90 days	20[b] 6.5, 2[b]	200 ppm: moderate vacuolization of brain 65, 20 ppm: no adverse effects on clinical signs, growth, hematology or clinical chemistries	Kennedy et al., 1976c[c]
Rat/Osborne-Mendel	6-8 days	4, sex NR	10 mg/kg in corn oil single dose	10	No neurologic signs, brains histologically normal	Ulsamer et al., 1975
	2-4 days	103, sex NR	10 mg/kg in corn oil for up to 42 days of age	10	Vacuolization in brain severe at 15 to mild at 42 days
	4 days	5, sex NR	10 mg/kg in corn oil for 13-22 doses	10	No clinical signs, no histopathological lesions
	10-13 days	30, sex NR	10 mg/kg in corn oil for 3 doses	10	Mild vacuolization
	22 days	6, sex NR	10 mg/kg in corn oil for 22-23 doses	10	No clinical signs, no histopathological lesions
Rat/CFN Z11	weanlings	10-12/group, females	0, 10, 20 or 30 mg/kg/day in 2% gum arabic 5 days/week for up to 10 weeks	0, 7.1, 14.3 or 21.4[d]	≥14.3 mg/kg/day: increased reaction time to hot plate test, decreased time on rotating rod test; spongiform encephalopathy in brain and spinal cord 7.1 mg/kg/day: no effects on behavior, lesions in CNS not identified with certainty	Alder and Zbinden, 1973; Zbinden and Alder, 1973

TABLE 5-4 (cont.)

Species/ Strain	Age	Number, Sex	Dosage Level, Vehicle Duration of Treatment	Transformed Dose (mg/kg/day)	Effects	Reference
Rat/Long-Evans	adult	NR, female	0, 1, 5, 10, 25 mg/kg/day in corn oil for 30 days	0, 1, 5, 10 or 25	25 mg/kg/day: deterioration of avoidance responding behavior; no effects on behavior at lower levels	Weiss et al., 1973, 1978
Rat/Charles River	NR	5/sex/group	0, 100 or 200 ppm in diet for 14 days	0, 5 or 10[e]	200 ppm: slightly elevated liver weight in females; no effects on in vitro microsomal detoxification of EPN or O-demethylation activities at either dose level.	Kennedy et al., 1975d[c]
Mice/Swiss	NR	15 females/ group	0, 100 or 200 ppm in diet for 30 days	0, 13 or 26[f]	100 ppm: reduced pentobarbital sleeping time 200 ppm: no effects on pentobarbital sleeping time	Kennedy et al., 1975d[c]
Monkey/ squirrel	young adult	2 females/ group	0, 1, 5 or 15 mg/kg in oil for 28 days	0, 1, 5 or 15	All dose levels: increase in primary component of visually evoked potential; decreased frequency of EEG; no histopathological lesions	Santolucito, 1972
Dog/beagle	NR	NR	30 ppm in diet for 13 weeks	0.75[g]	Swollen salivary gland, status spongiosus in brain and optic nerves	IRDC, 1974
Pig/Duroc	3 days	2-4, sex NR	0, 0.1, 0.5, 1, 2, 3, 4, 5, 15 or 45 mg/kg/day in corn oil for 36 days	0, 0.1, 0.5, 1, 2, 3, 4, 5, 15, 45	≥15 mg/kg/day: all died within 24 hours of first dose 4-5 mg/kg/day: 5/7 had neurological signs, 4/7 had CNS lesions, 4 died 1-2 mg/kg/day: 2/7 had signs, 4/7 had lesions, 1 died 0.5 mg/kg/day: 1 of 2 had mild signs, no lesions ≤0.1 mg/kg/day: no signs or lesions in 7	Robinson et al., 1975

[a]Assumed: young rats eat food in amount equivalent to 10% of their body weight/day (Mitruka et al., 1976).
[b]Transformed doses calculated by authors based on food consumption and body weight data.
[c]Study performed at IBT Laboratories
[d]TWA
[e]Assumed: adult rats eat food in amount equivalent to 5% of their body weight/day (U.S. EPA, 1980).
[f]Assumed: mice eat food in amount equivalent to 13% of their body weight/day (U.S. EPA, 1980).
[g]Transformed dose provided in review by Mahfouz (1982)
NR = Not reported

chemistries at low doses (≤6.5 mg/kg/day) and these are not considered to be sensitive endpoints for evaluating the toxicity of hexachlorophene (Kennedy et al., 1976c).

An age-related response to hexachlorophene among many species has been noted by several investigators, but has been quantitatively assessed most effectively by Ulsamer et al. (1975). These investigators administered hexachlorophene in corn oil by gavage to rats at 2-4, 4, 6-8, 10-13 or 22 days of age. Generally, clinical signs of neurologic dysfunction and CNS lesions occurred earlier and with greater severity in 2- to 4-day-old rats. The severity of the signs and lesions lessened as treatment was continued; mild lesions and signs were noted in 10- to 13-day-old rats. In rats started on treatment at 22 days of age, clinical signs and CNS lesions were absent. The very young appear to be a subgroup at special risk.

Exposure to hexachlorophene appears to alter behavior parameters in rats. In a study in weanlings, increased reaction time on the hot plate test and decreased time on the rotating rod test were observed at 14.3 mg/kg/day (Alder and Zbinden, 1973; Zbinden and Alder, 1973). Degenerative lesions in the CNS were also observed. These effects were not noted at 7.1 mg/kg/day. In a study in adult rats a deterioration of avoidance responding behavior occurred at 25 but not at ≤10 mg/kg/day (Weiss et al., 1973, 1978). Histopathological examinations were not performed.

At IBT Laboratories, Kennedy et al. (1975d) studied the effect of hexachlorophene on liver function of rats and mice. In rats, no effect on *in vitro* microsomal detoxification of EPN or O-demethylation activities occurred at 5 or 10 mg/kg/day for 14 days. In mice, 30 days treatment at 13 mg/kg/day reduced pentobarbital sleeping time. No effects on pentobarbital sleeping time occurred at 26 mg/kg/day.

The effect of hexachlorophene on the EEG has been studied in monkeys treated at 1, 5 or 15 mg/kg/day for 28 days (Santolucito, 1972). At all dose levels there was an increase in the primary component of the visually-evoked potential and a decrease in the mean frequency of the EEG.

As noted by Mahfouz (1982), beagle dogs in the IRDC (1974) study appear to be more sensitive than rats to the neurotoxic effects of hexachlorophene; at 30 ppm (0.75 mg/kg/day) in the diet for 13 weeks, dogs had swollen salivary glands and status spongiosus in the brain and optic nerves. Additional details were not provided.

An experiment with newborn pigs suggests that this species may be more sensitive than the other animals studied. In this experiment 3-day-old pigs were treated daily with 0, 0.1, 0.5, 1, 2, 3, 4, 5, 15 or 45 mg/kg/day for up to 36 days (Robinson et al., 1975). All 15 and 45 mg/kg/day pigs died following one dose. At 4 and 5 mg/kg/day, all seven piglets developed neurological signs or CNS lesions and four died. Neurological lesions or signs occurred in four of seven at the 1 or 2 mg/kg/day dose. Two pigs were maintained at 0.5 mg/kg/day. Of these, one reportedly had mild neurological signs but neither piglet had CNS lesions. An important observation made by the authors was that exposed pigs apparently gained resistance as treatment was continued. This is substantiated by the fact that no deaths occurred beyond day 8 of exposure and that tissue levels of hexachlorophene were lower in survivors than in those that had died.

5.6. OTHER RELEVANT INFORMATION

LD_{50} values (mg/kg) for hexachlorophene in several species and several routes of administration are listed in Table 5-5. Most noteworthy is the marked variation in the oral LD_{50} values in rats estimated by different laboratories (Hanig et al., 1977; Dymin et al., 1984; Nieminen et al., 1973;

TABLE 5-5

LD_{50} Values for Hexachlorophene

Route	Species	Age	LD_{50} (mg/kg)	Reference
Oral	rat	NR	180	Hanig et al., 1977
		NR	200	Dymin et al., 1984
		adult	~55	Nieminen et al., 1973
		adult	56-66	O'Donoghue, 1985
		weanling	87-120	O'Donoghue, 1985
		32 days	111	Nieminen et al., 1973
		10 days	80	Desi et al,. 1975
		10 days	9	Nieminen et al., 1973
		2 days	20	Desi et al., 1975
	mouse	NR	120	Dymin et al., 1984
	dog	2-3 weeks	15-30	Edds and Simpson, 1974
	pig	newborn	4	O'Donoghue, 1985
Dermal	rat	NR	1840	Dymin et al., 1984
	mouse	NR	1800	Dymin et al., 1984
Inhalation	rat	NR	340*	Dymin et al., 1984
	mouse	NR	290*	Dymin et al., 1984
i.v.	rat	adult	7.5	O'Donoghue, 1985
i.p.	rat	adult	21.8	O'Donoghue, 1985
		weanling	40	O'Donoghue, 1985

*The authors provided no data regarding exposure protocol or method of estimating inhaled dose.

NR = Not reported

O'Donoghue, 1985; Desi et al., 1975). Generally, it appears that nursing rats may be more susceptible than adults and that weanlings may be slightly more resistant than adults. LD_{50} values in mice (Dymin et al., 1984) and dogs (Edds and Simpson, 1974) are comparable to those in rats, but a lower LD_{50} value was reported for newborn pigs (O'Donoghue, 1985) indicating that pigs may be slightly more sensitive to the acute effects of orally administered hexachlorophene.

Hexachlorophene appears to be substantially less toxic to rats and mice when applied dermally, compared with oral administration (Dymin et al., 1984). Administration to rats by the i.v. or i.p. routes results in LD_{50} values lower than when administration is by the oral route (O'Donoghue, 1985). Dymin et al. (1984) reported inhalation LD_{50}s for hexachlorophene, but the exposure protocol and method of estimating inhaled dose were not reported, hence interpretation of these data is not possible.

A large body of data exists regarding the toxicity of hexachlorophene in humans. These data are not useful for risk assessment because exposures are acute and are not well quantified. Accidental poisoning by the oral route has been reported in an 8-day-old infant (Herskowitz and Rosman, 1979) and a 7-year-old boy (Martinez et al., 1974). Severe GI irritation, vomiting and diarrhea, and neurological signs such as twitching, lethargy, paresthesia, jitteriness and hypertonia were observed in both cases. The infant recovered without lasting signs of neurologic behavior. At autopsy, the 7-year-old showed severe degeneration of the optic nerve. The authors (Martinez et al., 1974) concluded that disruption of the optic nerves depended upon exposure by the oral route. Two reviews by Powell and Lampert (1979) and Kimbrough (1976) provide further data regarding accidental oral intoxication in humans.

Considerably more data exists regarding the dermal toxicity of hexachlorophene (Kopelman, 1973; Cunningham and Tsoulos, 1972; Nagy and Orosz, 1984; Anderson et al., 1975, 1981; Shuman et al., 1974b, 1975; Gowdy and Ulsamer, 1976; Plueckhahn and Collins, 1976; Chilcote et al., 1972, 1977; Larr'egue et al., 1984; Goutieres and Aicardi, 1977). Most of these studies and case histories are associated with the exposure of neonatal infants to liquid preparation of hexachlorophene used in baths. In healthy infants of normal birthweights, gestational age and vitality, often no clinical symptoms occur even though hexachlorophene is found in the blood (Cunningham and Tsoulos, 1972; Kopelman, 1973). The majority of the cases in which hexachlorophene-associated deaths occurred involved premature infants of low birthweights (Plueckhahn and Collins, 1976; Shuman et al., 1974b, 1975; Anderson et al., 1975, 1981) or those suffering from severe hepatic insufficiency (Plueckhahn and Collins, 1976). The lesions observed in the brain upon autopsy were classified as vacuolar encephalopathy or spongiform myelinopathy, and were attributed solely to exposure to hexachlorophene.

Gowdy and Ulsamer (1976), however, examined the brains of 135 infants that were stillborn or died within a few days of birth. Although vacuolization was observed in all brains in which hexachlorophene was identified, vacuolization was also seen in brains from which hexachlorophene was not identified. There was a slight but not statistically significant correlation between brain and tissue content and severity of vacuolization. The authors cautioned that vacuolization in the brain is not pathognomonic for hexachlorophene toxicity but may result from exposure to a number of chemicals.

Chilcote et al. (1972, 1977) reported the case of a 10-year-old male burn patient who progressed satisfactorily early in the course of his

recuperation but then developed neurologic symptoms and died. He had been bathed daily in hexachlorophene to control infection. Autopsy examination revealed "toxic levels" of hexachlorophene in serum and tissues and edema of many regions of the brain.

Dermal application of dry forms of hexachlorophene have also led to toxicity and death (Goutieres and Aicardi, 1977; Larr'egue et al., 1984). In this case, accidental poisoning of 18 young children occurred from application of a powder containing 6% hexachlorophene. Signs of toxicity were attributed to intercranial hypertension and spinal cord damage, the result of intramyelinic edema. Autopsy examination performed on the four who died revealed severe spongiform degeneration of the CNS with edema, demyelination and hemorrhage in the spinal cord. All children developed an erythematous skin irritation at the site of application, which resembled "a short pair of red pants" (Larr'egue et al., 1984).

Asthma-like symptoms in a 43-year-old pediatric nurse were attributed to 15 years of exposure to hexachlorophene (Nagy and Orosz, 1984). The patient complained of respiratory symptoms of ~10 years duration. Symptoms began as a rhinitis and progressed chest tightness, breathlessness and asthmatic attacks. She was free of attacks during weekends and holidays.

5.7. SUMMARY

Hexachlorophene was negative for carcinogenicity in at least two strains of rats (NCI, 1978; Rudali and Assa, 1978; IRDC, 1980a) and at least two strains of mice (Rudali and Assa, 1978; IRDC, 1980b) in lifetime feeding experiments at dietary exposures $\leq$150 ppm. In addition, negative results were obtained in mice exposed during gestation or in the neonatal period. Lifetime skin painting tests were negative in mice and rabbits (Stenback, 1975, 1977).

Hexachlorophene was consistently negative for mutagenicity when tested in the S. typhimurium assay (Haworth et al., 1983; Arnold et al., 1975; Gocke et al., 1981), chromosomal aberration tests (Dymin et al., 1984; Gocke et al., 1981; Sobti et al., 1983), the dominant lethal test in male mice (Kennedy et al., 1975a; Arnold et al., 1975) and the sex-linked recessive test in D. melanogaster (Gocke et al., 1981). Positive results were noted only in experiments in two Eastern bloc countries: a test in S. typhimurium (Dymin et al., 1984) and a micronucleus test in mouse bone marrow cells (Syllanco, 1978); the data were not presented in either of these two reports.

Hexachlorophene has been determined to be teratogenic to rats treated orally (Oakley and Shepard, 1972; Kennedy et al., 1975b) or vaginally (Kimmel et al., 1972, 1973, 1974), in rabbits treated orally (Kennedy et al., 1975b) and in hamsters treated subcutaneously (Geber, 1977). Mice treated dermally exhibited fetotoxicity but not teratogenicity. The threshold for teratogenicity by the oral route appears to be ~25 mg/kg/day in rats (Oakley and Shepard, 1972) and ~6 mg/kg/day in rabbits (Kennedy et al., 1975b). In rats, a dose of 15 mg/kg/day is associated with fetotoxicity (Kennedy et al., 1976b; Haley et al., 1973). Maternal toxicity is also associated with the same dose levels that cause teratogenicity.

Hexachlorophene has been implicated as a human teratogen, primarily because of retrospective studies of malformed infants born to Swedish hospital workers exposed to the chemical (Halling, 1975, 1977). A subsequent and longer epidemiological study, however, failed to find an increased incidence of malformed infants born to hexachlorophene-exposed hospital workers (Baltzar et al., 1979a).

In a reproduction study, hexachlorophene at 10 mg/kg/day by gavage (Kennedy et al., 1976b) reduced the survival of 12- and 21-day-old offspring

in rats. In a 3-generation feeding study in rats, decreased numbers of corpora lutea and implantations, decreased numbers of F_{1a} pups surviving until lactation day 4 and decreased body weight of pups were observed at 60 ppm (IRDC, 1979). Hexachlorophene administered orally to mature male dogs and rats at ≥3 mg/kg/day for 9 weeks or to rats at single doses ≥75 mg/kg brought about a rapid but transitory reduction in spermatogenesis and degeneration of the germinal epithelium of the testis (Thorpe, 1967; James et al., 1980). Hexachlorophene administered s.c. to neonatal hamsters (Alleva, 1973) or dermally to rats (Gellert et al., 1978) had no effect on the subsequent sexual maturation or fertility of the hamsters or female rats. Male rats, however, had severely depressed fertility, primarily resulting from an inability to ejaculate. Spermatogenesis appeared to be normal.

Chronic toxicity tests with hexachlorophene include the NCI (1978) bioassay in rats, the Rudali and Assa (1978) assays in rats and mice and the IRDC (1980a,b) studies in rats and mice. No adverse effects were noted at dietary levels ≤150 ppm in rats or mice and the NCI (1978) and Rudali and Assa (1978) studies. The only effect observed in the IRDC (1980a,b) studies was reduced body weight gain in rats fed 100 ppm; food consumption data were not reported. Adverse effects were observed at lower doses in subchronic studies.

The central and peripheral nervous system and the retina (an extension of the nervous system) appear to be the target tissues for the toxicity of hexachlorophene, as shown by several short-term studies performed at high doses. Subchronic oral studies in rats appear to define the following thresholds: death at 28.9 mg/kg/day, slowly reversible neurologic dysfunction at 14.9 mg/kg/day, reduced rate of body weight gain at 7.7 mg/kg/day (Nakaue et al., 1973) and histopathological lesions in the nervous system at

5 mg/kg/day (Jones et al., 1974). These data suggest a relatively steep dose response curve for hexachlorophene. Neonates tend to be more sensitive than older nursing or adult rats (Ulsamer et al., 1975). Beagle dogs appear to be more sensitive than rats; at 30 ppm (0.75 mg/kg/day) in the diet for 13 weeks, dogs had status spongiosus in the brain and optic nerve (IRDC, 1974).

Newborn pigs appear to be more sensitive than other species, as the threshold for death and histopathological lesions of the brain appears to be at 1-2 mg/kg/day and the threshold for mild neurological signs appears to be 0.5 mg/kg/day (Robinson et al., 1975).

Oral LD_{50} values in rats range from 9-20 mg/kg/day with adults being more resistant than neonates (Nieminen et al., 1973; Dymin et al., 1984). Pigs appear to be the most susceptible species tested, as the oral LD_{50} is 4 mg/kg for newborn pigs (O'Donoghue, 1985).

The neurological signs and histopathological lesions produced in humans by accidental oral or dermal intoxication resemble closely those observed in experimentally poisoned animals. In cases of oral poisoning, severe GI signs also occur (Powell and Lampert, 1979; Kimbrough, 1976). The majority of human toxicity cases involve dermal exposure. Neonatal infants appear to be the subpopulation at greatest risk (because their skin is more permeable and they were bathed in hexachlorophene more frequently), and their susceptibility is increased by reduced birthweight, short gestation age or impaired liver function (Shuman et al., 1974b, 1975; Anderson et al., 1975, 1981; Plueckhahn and Collins, 1976). Premature infants of low birthweight or who suffer from impaired liver function appeared to be at greatest risk (Shuman et al., 1974b, 1975; Pleuckahn and Collins, 1976). Burn victims are also at high risk to the dermal application of hexachlorophene (Chilcote et al., 1972, 1977).

6. AQUATIC TOXICITY

6.1. ACUTE

Dive et al. (1980) determined that the MAD for population growth inhibition of the ciliate protozoan, Colpidium campylum, was 0.3 mg/ℓ.

Morgan et al. (1972) conducted a 96-hour bioassay with bluegills, Lepomis macrochirus, using hexachlorophene dissolved in acetone. Concentrations of ≥0.56 mg/ℓ caused 100% mortality within 24 hours. All fish survived 0.10 mg/ℓ for 96 hours.

6.2. CHRONIC

Webster et al. (1974) exposed Xenopus tadpoles to 0.2 mg/ℓ hexachlorophene for 1-7 days. The myelin sheath of nervous tissue was affected to various degrees depending on duration of exposure. After 8 hours of exposure to 0.2 mg/ℓ, abnormalities in posture and swimming were observed, and they persisted for the length of the experiment.

Hattori et al. (1984) reported an EC_{50} of 0.008 mg/ℓ for inhibition of Daphnia carinata reproduction.

6.3. PLANTS

Pertinent data regarding the toxicity of hexachlorophene to aquatic plants could not be located in the available literature as cited in the Appendix.

6.4. RESIDUES

In a study using Xenopus tadpoles, hexachlorophene was absorbed rapidly, with concentrations in tadpoles 10 times that of the surrounding medium after 1 day (Webster et al., 1974). The highest levels were found in the myelin sheath of nerve fibers. Tadpoles exposed to 0.1 mg/ℓ achieved whole body concentrations of 3.4 mg/kg, while those exposed to 0.2 mg/ℓ achieved 17.1 ppm after 3 days.

A field study also indicated that hexachlorophene accumulated in tissues of aquatic organisms. Sims and Pfaender (1975) analyzed for hexachlorophene residues in water, sediments, and tissues of aquatic invertebrates in a stream below sewage outfalls. Although small numbers of individual organisms were examined, they showed significantly higher hexachlorophene concentrations than water or sediment (Table 6-1). Considerable biomagnification appeared to have occurred in the crayfish, water boatmen, and water scavengers. Water boatmen, Sigara sp., had hexachlorophene concentrations 1000 times greater than the surrounding water.

6.5. SUMMARY

Concentrations of hexachlorophene $\geq$0.56 mg/ℓ caused 100% mortality in bluegill fish within 24 hours (Morgan et al., 1972). No deaths occurred at 0.10 mg/ℓ for 96 hours. The LC_{50} values were 0.29, 0.24 and 0.18 mg/ℓ for 24, 48 and 96 hours, respectively. Hexachlorophene is quite toxic to Daphnia magna, inhibiting reproduction at 0.008 mg/ℓ (Hattori et al., 1984). It is also subject to bioaccumulation (Webster et al., 1974) and biomagnification (Sims and Pfaender, 1975).

TABLE 6-1

Hexachlorophene Concentrations in Water, Sediments and Aquatic Invertebrates in Upper Haw River Basin, NC*

Specimen	Number of Samples	Hexachlorophene Concentration (ppb)
Surface water	15	16.4-44.3
Bottom water	12	16.4-48.3
Sediments	13	9.3-377.0
Sludge worms (*Tubifex tubifex*)	4	335
Water scavengers (*Hydrophilus triangularis*)	1	<1,500
Crayfish (immature Cambarinae)	2	1,338
Water boatmen (*Sigara* sp.)	2	27,800

*Source: Sims and Pfaender, 1975

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The Code of Federal Regulations (1982) lists a tolerance of 0.05 ppm for hexachlorophene in or on raw cottonseed, resulting from the use of the monosodium salt as a fungicide on the crop before the bolls are open. It is further specified that the hexachlorophene used in the formulation must not contain more than 1 ppm 2,3,7,8-TCDD.

On September 27, 1972, the U.S. FDA issued revised rules and regulations regarding the production, sale and use of hexachlorophene-containing drugs and cosmetics (Anonymous, 1972; U.S. FDA, 1972). Dusting powders for infants containing >0.75% were immediately recalled and other products containing >0.75% became available only by prescription. Cosmetics and drugs containing $\leq$0.75% were not recalled but further production and shipment was banned. When used as a preservative in cosmetics and other drugs, a level of 0.1% is permitted.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of azobenzene could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Hexachlorophene was negative for carcinogenicity in at least two strains of rats (NCI, 1978; Rudali and Assa, 1978; IRDC, 1980a) and at least two strains of mice (Rudali and Assa, 1978; IRDC, 1980b) in lifetime feeding experiments using dietary levels ≤150 ppm. In addition, negative results were obtained in mice exposed during gestation or in the neonatal period. Lifetime skin painting tests were negative in mice and rabbits (Stenback, 1975, 1977).

Hexachlorophene was consistently negative for mutagenicity when tested in the S. typhimurium assay (Haworth et al., 1983; Arnold et al., 1975; Gocke et al., 1981), chromosomal aberration tests (Dymin et al., 1984; Gocke et al., 1981; Sobti et al., 1983), the dominant lethal test in male mice (Kennedy et al., 1975a; Arnold et al., 1975) and the sex-linked recessive test in D. melanogaster (Gocke et al., 1981). Positive results were noted only in two experiments: a test in S. typhimurium (Dymin et al., 1984) and a micronucleus test in mouse bone marrow cells (Sylianco, 1978); the data were not presented in either of these two reports.

Hexachlorophene has been determined to be teratogenic to rats treated orally (Oakley and Shepard, 1972; Kennedy et al., 1975b) or vaginally (Kimmel et al., 1972, 1973, 1974), in rabbits treated orally (Kennedy et al., 1975b) and in hamsters treated s.c. (Geber, 1977). Mice treated dermally exhibited fetotoxicity but not teratogenicity. The threshold for teratogenicity by the oral route appears to be ~25 mg/kg/day in rats (Oakley and Shepard, 1972) and ~6 mg/kg/day in rabbits (Kennedy et al., 1975b). In rats, a dose of 15 mg/kg/day is associated with fetotoxicity (Kennedy et al., 1976b; Haley et al., 1973). Maternal toxicity is also associated with the same dose levels that cause teratogenicity.

Hexachlorophene has been implicated as a human teratogen, primarily because of retrospective studies of malformed infants born to Swedish hospital workers exposed to the chemical (Halling, 1977, 1979). A subsequent and longer epidemiological study, however, failed to find an increased incidence of malformed infants born to hexachlorophene-exposed hospital workers (Baltzar et al., 1979a).

In a reproduction study, hexachlorophene at 10 mg/kg/day by gavage (Kennedy et al., 1976b) reduced the survival of 12- and 21-day-old offspring in rats. In a 3-generation feeding study in rats, decreased numbers of corpora lutea and implantations, decreased numbers of F_{1a} pups surviving until lactation day 4 and decreased body weights of pups were observed at 60 ppm (IRDC, 1979). Hexachlorophene administered orally to mature male dogs and rats at $\geq$3 mg/kg/day for 9 weeks or to rats at single doses $\geq$75 mg/kg brought about a rapid but transitory reduction in spermatogenesis and degeneration of the germinal epithelium of the testis (Thorpe, 1967; James et al., 1980). Hexachlorophene administered subcutaneously to neonatal hamsters (Alleva, 1973) or dermally to rats (Gellert et al., 1978) had no effect on the subsequent sexual maturation or fertility of the hamsters or female rats. Male rats, however, had severely depressed fertility, primarily resulting from an inability to ejaculate. Spermatogenesis appeared to be normal.

Chronic toxicity tests with hexachlorophene include the NCI (1978) bioassay in rats, the Rudali and Assa (1978) bioassays in rats and mice and the IRDC (1980a,b) studies in rats and mice. No adverse effects were noted at dietary levels $\leq$150 ppm in rats or mice in the NCI (1978) and Rudali and Assa (1978) studies. The only effect observed in the IRDC (1980a,b) studies was reduced body weight gain of rats fed 100 ppm; food consumption data were

not reported. Adverse effects were observed at lower doses in subchronic studies. In rats, Ulsamer et al. (1975) and Nakaue et al. (1973), and in pigs, Robinson et al. (1975) suggested that animals exposed continuously to hexachlorophene develop tolerance and transient signs or mild lesions disappear with time and continued treatment.

The central and peripheral nervous system and the retina appear to be the target tissues for the toxicity of hexachlorophene, as shown by several short-term studies performed at high doses. Subchronic oral studies in rats appear to define the following thresholds: death at 28.9 mg/kg/day, slowly reversible neurologic dysfunction at 14.9 mg/kg/day, reduced rate of body weight gain at 7.7 mg/kg/day (Nakaue et al., 1973) and histopathological lesions in the nervous system at 5 mg/kg/day (Jones et al., 1974). These data suggest a relatively steep dose response curve for hexachlorophene. Neonates tend to be more sensitive than older nursing or adult rats (Ulsamer et al., 1975). Beagle dogs appear to be more sensitive than rats; at 30 ppm (0.75 mg/kg/day) in the diet for 13 weeks, dogs had status spongiosus in the brain and optic nerve (IRDC, 1974). A LOAEL and NOAEL for dogs have not been established.

Newborn pigs appear to be the most sensitive animals tested, as the threshold for death and histopathological lesions of the brain appears to be 1-2 mg/kg/day and the threshold for mild neurological signs appears to be 0.5 mg/kg/day (Robinson et al., 1975). No effects were noted at 0.1 mg/kg/day. This study can be faulted because exposure was for a relatively short period of time, 36 days, because small numbers of piglets were used at each dosage level and because the piglets were housed with the dams, predisposing them to death or injury by the dam. In spite of these shortcomings, a definite dose-response pattern was observed. Exposure at 1-2 mg/kg/day

clearly resulted in adverse effects and exposure at 0.1 mg/kg/day clearly did not. The dose of 0.75 mg/kg/day in dogs at which similar effects were observed is intermediate between 1 mg/kg/day and the LOAEL of 0.5 mg/kg/day in pigs. At 0.5 mg/kg/day, one of two piglets had mild signs of neurotoxicity, but no microscopically observed lesions. Although a LOAEL for neurotoxic effects has not been established for dogs, the effect (status spongiosus) at 0.75 mg/kg/day with no clinical signs of neurotoxicity is less severe than the overt signs of neurotoxicity in the pigs at 0.5 mg/kg/day. It is reasonable, therefore, that the LOAEL in dogs would fall within the range of 0.1-0.5 mg/kg/day.

The NOEL of 0.1 mg/kg/day in pigs, therefore, can be chosen with reasonable confidence for the basis of the ADI. Dividing the NOEL of 0.1 mg/kg/day by an uncertainty factor of 100 (10 to extrapolate experimental animal data to humans and 10 to account for sensitive subgroups) results in an ADI of 0.001 mg/kg/day or 0.07 mg/day for a 70 kg human.

Ordinarily, an uncertainty factor would be included to extrapolate from subchronic to chronic data. Chronic bioassays in two strains each of rats and mice at 150 ppm (7.5 mg/kg/day for rats, 19.5 mg/kg/day in mice) failed to reveal any treatment-related adverse effects. The research of several investigators revealed that the effects of hexachlorophene on the nervous system are reversible when treatment is terminated (DeJesus and Pleasure, 1973; Powell et al., 1978; Cammer et al., 1975; Kimbrough and Gaines, 1971; Benitz et al., 1974; Lampert et al., 1973; Kennedy et al., 1976b). Furthermore, Ulsamer et al. (1975) showed that adaptation to hexachlorophene occurs and that signs and lesions develop in 2- to 3-day-old rats that disappear even as treatment is continued. It does not seem necessary, therefore, to apply an uncertainty factor for extrapolation from subchronic to chronic exposure.

Hexachlorophene has been established as an animal teratogen and fetotoxin (Oakley and Shepard, 1972; Kennedy et al., 1975b; Kimmel et al., 1972, 1973, 1974; Geber, 1977). These adverse effects have only been demonstrated at dosage levels also associated with maternal toxicity, $\geq$15 mg/kg/day. Reduced survival of rat offspring was observed in a dietary reproduction study at 100 ppm (5.0 mg/kg/day, assuming rats eat food equivalent in amount to 5% of their body weight/day (Gaines et al., 1973; Gaines and Kimbrough, 1971) and in a gavage study at 10 mg/kg/day (Kennedy et al., 1976b). Reduced numbers of corpus lutea and implantations, reduced survival to day 4 of lactation and reduced body weight of pups observed in rats at a dietary level of 60 ppm (3 mg/kg/day) in the 3-generation study by IRDC (1974). Effects on male reproduction were demonstrated at substantially higher doses that were also associated with subchronic toxicity (Thorpe, 1967; James et al., 1980). Since teratogenicity, fetotoxicity and effects on reproduction are associated with doses substantially larger than the NOAEL from which the ADI is derived. the ADI is proffered with confidence that it should be protective against these effects as well as against the effects of chronic and subchronic toxicity.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Several subchronic toxicity and teratogenicity studies, reviewed in Sections 5.3. and 5.5., are appropriate for deriving human MEDs, CSs and RQs. In addition, studies of the effects on reproduction, reviewed in Section 5.4., are also useful for derivation of CSs. These studies are summarized in Tables 5-4 and 9-1. The chronic cancer bioassays in rats and mice reviewed in Section 5.5. are not useful for derivation of a CS because the only effect reported was reduced body weight gain of rats treated with 100 ppm hexachlorophene in the diet (IRDC, 1980a). This effect is less serious than those described at lower doses in subchronic studies.

As seen from Tables 5-4 and 9-1, the major effects associated with hexachlorophene intoxication are teratogenicity (Oakley and Shepard, 1972; Kennedy et al., 1975b), reduced survival of offspring to weaning (Gaines et al., 1973; Gaines and Kimbrough, 1971), neurological signs and lesions of the nervous system (IRDC, 1974; Nakaue et al., 1973; Robinson et al., 1975). Based on the lowest doses at which these effects occurred in several species, human MEDs, CSs and RQs are calculated for these effects and presented in Table 9-2. Human MEDs were calculated by multiplying the animal doses by the cube root of the ratio of the body weight of the animal to that of man and multiplying the result by 70 kg to express the MED in terms of mg/day for a 70 kg human. No uncertainty factor was applied to convert from subchronic to chronic exposure because evidence reviewed in Chapter 8 suggests that animals develop tolerance with continued exposure.

TABLE 9-1

Summary of Oral Teratogenicity and Reproductive Studies of Hexachlorophene in Laboratory Animals

Species/Strain	Number, Sex	Dosage Level, Vehicle, Duration of Treatment	Transformed Dose (mg/kg/day)	Effects	Reference
Rat/NR	4 females	500 ppm in the diet on gestation days 7 or 8-20	25[a]	Small feluses and cleft palate; maternal toxicity (neurological signs)	Oakley and Shepard, 1972
Rabbit/New Zealand white	9-52 females/ group	0, 3 or 6 mg/kg in aqueous methylcellulose on days 6-18 of gestation	6	Small but not statistically significant increase in incidence of acrania and minor skeletal malformations, feto1oxicity (resorptions) and maternal toxicity (reduced rate of body weight gain)	Kennedy et al., 1975b[b]
Rat/CD®S	20 females/ group	0, 15, 30 mg/kg/day in aqueous methylcellulose from gestation day 15 throughout lactation	30 15	Increased number of stillborn; maternal mortality; reduced survival at weaning; no maternal toxicity	Kennedy et al., 1976b; Haley et al., 1973[b]
Rat/Sherman	10/sex/group	100 ppm in diet starting at 4-5 weeks of age through 2 generations	5[a]	Reduced survival to weaning, status spongiosus in brain of F_{1b} but not F_{2a}	Gaines et al., 1973; Gaines and Kimbrough, 1971
Rat/NR	NR/NR	60 ppm in diet for 3 generations	3	Decreased numbers of corpora lutea, decreased F_{1a} pups surviving until lactation day 4; decreased body weight of pups	IRDC, 1979

[a]Assumed: rats eat food equivalent in amount to 5% of their body weight/day

[b]Experiment performed at IBT Laboratories

NR - Not reported

TABLE 9-2

Composite Scores for the Toxicity of Orally Administered Hexachlorophene

Species	Animal Dose (mg/kg/day) Duration	Human MED (mg/day)[a]	RV_d	Effect	RV_e	CS	RQ	Reference
Rat	25 on days 7 or 8-20 of gestation	299	1.8	Teratogenicity with maternal toxicity	9	16.2	1000	Oakley and Shepard, 1972
Rabbit	6 on days 6-18 of gestation	159	2.2	Teratogenicity with maternal toxicity	9	19.8	1000	Kennedy et al., 1975b[b]
Rat	6 for 3 generations	72	2.7	Decreased number of corpora lutea	8	21.6	100	IRDC, 1979
Rat	5 for 2 generations	60	2.8	Reproductive dysfunction; reduced survival at weaning	10	28	100	Gaines et al., 1973; Gaines and Kimbrough, 1971
Rat	14.9 for 16 weeks	178	2.1	Transient neurological deficit	8	16.8	1000	Makaue et al., 1973
Rat	7.7 for 16 weeks	92	2.6	Cerebral edema and vacuolization without evidence of neurological dysfunction	6	15.6	1000	Makaue et al., 1973
Dog	0.75 for 90 days	29.7	3.3	Status spongiosus in brain and optic nerve	6	19.8	1000	IRDC, 1974
Piglet	4 for 36 days	103	2.4	Death	10	24	100	Robinson et al., 1975
Piglet	1 for 36 days	26	3.4	Neurological deficit and lesions	9	30.6	100	Robinson et al., 1975
Piglet	0.5 for 36 days	12.9	3.8	Mild neurological signs	8	30.4	100	Robinson et al., 1975

[a]Calculated by multiplying the animal effective dose in mg/kg/day by the cube root of the ratio of the body weight of the experimental animal to the reference body weight of man (70 kg), and by 70 kg to express the MED as mg/day. Assumed animal body weights: rat, 0.35 kg (U.S. EPA, 1980); rabbit 3.8 kg (Durkin, 1985); dog, 12.7 kg (Durkin, 1985); newborn piglet, 3.5 kg (Brody, 1945). An uncertainty factor was not applied to convert subchronic to chronic data because evidence reviewed in Chapter 8 suggests that animals develop tolerance with continued exposure.

[b]Experiment conducted at IBT Laboratories

The CSs range from 16.2 associated with teratogenicity in rats (Oakley and Shepard, 1972) to 30.6 associated with neurologic deficits and CNS lesions in piglets (Robinson et al., 1975). Pigs appear to be more sensitive than rats to the effects of hexachlorophene and the highest CS of 30.6 reflects this observation. The CS of 30.6, corresponding to an RQ of 100, is chosen to most stringently represent the toxicity of hexachlorophene (Table 9-3).

In a previous RQ determination for hexachlorophene, the U.S. EPA (1983) derived CSs for the effects of hexachlorophene based on the 2-generation reproduction study in rats by Gaines et al. (1973) and a 70- to 98-day study in which rats exposed to 25 mg/kg/day developed severe neurologic dysfunction and lesions in the brain (Kimbrough and Gaines, 1971). The CS calculated for reduced survival of offspring by the U.S. EPA (1983) agrees with that derived in this document.

In this document, pigs are shown to be more sensitive than rats to the effects of hexachlorophene. The Robinson et al. (1975) pig study was apparently omitted from the 1983 documents. For reasons previously discussed, it was not deemed necessary to apply an uncertainty factor to extrapolate from subchronic to chronic exposure based on the more extensive literature review provided in the present document. Despite these differences, the U.S. EPA (1983) chose a CS of 29.5, associated with an RQ of 100 pounds based on neurotoxicity and brain lesions in rats, to represent the toxicity of hexachlorophene. The CS of 30.6 derived from the pig study also corresponds to an RQ of 100 pounds. The previous CS of 29.5 is essentially indistinguishable from the current calculation of 30.6. However, in order to stringently conform to the RQ methodology the CS of 30.6 is presented in the present document.

TABLE 9-3

Hexachlorophene

MINIMUM EFFECTIVE DOSE (MED) AND REPORTABLE QUANTITY (RQ)

Route:	oral
Dose*:	26 mg/day
Effect:	neurological dysfunction and CNS lesions
Reference:	Robinson et al., 1975
RV_d:	3.4
RV_e:	9
Composite Score:	30.6
RQ:	100

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*Equivalent human dose

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Hexachlorophene was negative for carcinogenicity in at least two strains of rats (NCI, 1978; Rudali and Assa, 1978; IRDC, 1980a) and in at least two strains of mice (Rudali and Assa, 1978; IRDC, 1980b) in lifetime feeding experiments using dietary concentrations $\leq$150 ppm. In addition, negative results were obtained in mice exposed during gestation or in the neonatal period. Lifetime skin painting tests were negative in mice and rabbits (Stenback, 1975, 1977). Data were not located implicating hexachlorophene as a human carcinogen. The lack of positive carcinogenicity data precludes the derivation of a potency factor for hexachlorophene.

Because of the lack of data, IARC (1979) has declined to make an evaluation of the potential for carcinogenicity of hexachlorophene. A designation of Group 3, not classified, is most appropriate. Although the carcinogenic bioassays for hexachlorophene were negative, there is indication that higher doses of the test compound could have been employed in the studies, thus enhancing the possibility of observing a tumor response, if in fact one occurs, with the limited number of animals tested. In one rat study, dosing was not started until the animals had reached 6 months of age. Younger animals are generally considered to be susceptible to carcinogens. In some other studies, the treatment was not carried out for the lifetime of the animals. Because of these shortcomings in the cancer assays, the animal evidence for the carcinogenicity of hexachlorophene is considered to be inadequate. Based on U.S. EPA (1984) guidelines for carcinogen risk assessment and unavailability of human data, the overall weight of evidence classification is Group D, meaning hexachlorophene cannot be classified as a human carcinogen. It should be noted that hexachlorophene may be contaminated with the highly toxic chemical 2,3,7,8-TCDD (dioxin), considered by the U.S. EPA to be a probable human carcinogen.

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN Internation
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in August, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

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